EXPERT REVIEWS

# Achalasia: current treatment options

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Achalasia is a rare esophageal motility disorder, characterized by impaired swallow-induced, lower esophageal sphincter (LES) relaxation and defective esophageal peristalsis. Unfortunately, there are no etiological therapies for achalasia. Patients present with dysphagia, chest pain and regurgitation of undigested food, often leading to weight loss. The currently available treatments have the common aim of relieving symptoms by decreasing the pressure of the LES. This can be achieved with some medications, by inhibiting the cholinergic innervation (botulinum toxin), by stretching (endoscopic dilation) or cutting (surgery) the LES. Recently, other therapeutic options, including per-oral endoscopic myotomy have been developed and are gaining international consensus. The authors report on the benefits and weaknesses of the different therapies and provide an updated approach to the management of achalasia.

**Keywords:** achalasia • botulinum toxin injection • dysphagia • esophageal manometry • esophageal myotomy • high-resolution manometry • POEM esophageal motility disorders, pneumatic balloon dilation • surgery

Esophageal achalasia is a rare disease that affects the esophageal motility. The loss of the ganglion cells in the myenteric plexus of the esophageal body and the lower esophageal sphincter (LES) is the pathophysiological hallmark of achalasia. This leads to esophageal wall aperistalsis, increased LES tone and absent relaxation of the LES in the act of deglutition. The leading clinical manifestation is progressive dysphagia, which can be accompanied by chest pain, heartburn and regurgitation. Impaired food transit through the esophagogastric junction (EGJ) can result in weight loss (late in the course of the disease) as well as complications of regurgitation (aspiration pneumonia, night-time coughing) and increased risk of developing esophageal cancer. Idiopathic achalasia is sporadic. Although more rare, achalasia can also be part of other complex syndromes, such as Allgrove syndrome, Down's syndrome or familial visceral neuropathy [1].

Achalasia is diagnosed by esophageal manometry. Demonstration of aperistalsis of the esophageal body and incomplete LES relaxation is diagnostic for achalasia. High-resolution manometry (HRM) shows better results compared to traditional manometry for the diagnosis of achalasia [2]. Studies have shown that based on the results of HRM, a classification of achalasia can be made into three distinct types [2]. This classification may be helpful in directing treatment, given the different clinical behavior of each achalasia subtype [3]. Additional assessment of achalasia includes barium swallow, which shows the degree of esophageal stasis and esophageal dilatation. Timed barium esophagogram is a simple and objective method for assessing esophageal emptying. The technique of timed barium esophagogram is similar to usual barium swallow with some modifications, which include taking multiple sequential films (usually at the end of the barium swallow, and after 1, 2 and 5 min) after a single swallow of a fixed volume (100–250 ml) of a specific density barium solution. Timed barium esophagogram is useful especially during the follow-up of the patients after treatment [4]. Esophagogastroduodenoscopy (EGD) is usually performed before any treatment to exclude cases of pseudo-achalasia caused by neoplasms, benign strictures, inflammation and infectious diseases.

There are no etiological therapies for achalasia. The current available treatments have the common aim of relieving dysphagia and other symptoms associated with achalasia, by decreasing the resting and swallow-induced residual LES pressure, thus improving




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esophageal emptying. Unfortunately, there is no therapy that can effectively cure the underlying conditions responsible for the disease and restore the normal muscle activity of the esophageal body and LES [1].

Traditional therapeutic options include medications, injection of botulinum toxin (BTI) into the LES, pneumatic balloon dilation (PD) of the LES and surgical myotomy (laparoscopic Heller myotomy [LHM] with or without fundoplication). All of the abovementioned treatments act on the basal pressure of the LES with different success rates, efficacy and complications. As a consequence, therapies should be tailored to the patient's general conditions, expectations and preferences (Table 1).

More favorable results in terms of success rates and long-term efficacy are reported for PD and LHM with partial anterior fundoplication [5,6].

In recent years, a novel less invasive endoscopic technique for the treatment of achalasia, the per-oral endoscopic myotomy (POEM), has been developed and its efficacy has been actively investigated [7].

In this manuscript, we report on the different therapeutic options for the management of esophageal achalasia, including established benefits and weaknesses of every single approach, with special focus on the most recent treatments.

## Medical therapy

Medical therapy has a very marginal role in the treatment of achalasia. LES pressure can be only partially reduced by smooth muscle relaxants. Nitrates and calcium channel blockers are the most used medications [1]. The phosphodiesterase-5-inhibitor, sildenafil, has also been shown to lower the LES pressure in patients with achalasia [1]. Their effect on LES is dose dependent. Medications should be taken 15–30 min before meals, preferably with sublingual preparations, because the esophagogastric transit can be slow in patients with achalasia.

However, the effect is usually incomplete, and the efficacy decreases substantially with time. Side effects, when the dose is increased, are common and include headache, hypotension and pedal edema. The role of such medications should be limited to a very occasional use (while patients are waiting to be operated) or in patients who refuse or cannot undergo operative treatment of achalasia. These drugs can also be used to occasionally treat spasms and chest pain after the operative treatment of achalasia.

## Botulinum toxin injection

The use of BTI for the treatment of achalasia was first described in 1995 by Pasricha *et al.* [8]. BTI is injected into the LES under direct endoscopic control. The drug inhibits the release of acetylcholine from excitatory nerve endings at this level, decreases LES pressure and improves esophageal emptying and achalasia symptoms.

Many series reported on the efficacy of BTI and its role in the management of achalasia [9]. BTI is easy, inexpensive and can be performed on patients with severe comorbidities. Because of these features, this method is one of the most common initial treatments of achalasia.

The technique of BTI has been described in the original study by Pasricha [8] and did not substantially change with time. A total of 80–100 U of BTI is injected in the four quadrants of the LES, in divided doses (20–25 U per quadrant). It is sometimes difficult to inject the solution precisely and deeply into the LES. In order to obtain a more homogeneous delivery of the BTI into the LES, some authors recommend to divide the solution in eight doses and inject them at four quadrants, at two different levels, with four injections into the LES and another four injections few centimeters above it. However, it is speculative to find substantial differences with the standard injection technique, in terms of clinical results and duration of the treatment [9].

A single injection of BTI is relatively effective in the short term, but the efficacy decreases with time and patients may require additional treatments. In a review article, BTI improved symptoms of patients in 79% at 1 month, 70% at 3 months, 53% at 6 months and only 41% at 12 months follow-up [6]. Treatment can be repeated, but the efficacy may be less marked. Antibodies against the core component can interfere and cause resistance to its therapeutic effect in up to 26% of patients [9]. Side effects and complications of BTI are anecdotal [9].

BTI remains an important treatment of achalasia, especially for elderly patients, or those with comorbidities, after failure of the medical therapy. In case of extreme need, BTI can also be performed as a bridge therapy, before a more long-standing treatment of achalasia. However, it has been reported that prior BTI can cause distal esophageal intramural inflammation and submucosal fibrosis, which makes a subsequent myotomy technically challenging [10]. However, strong evidence is still lacking about this issue [9]. No substantial problems were observed when BTI was performed before POEM [11–13].

Finally, BTI may be used for the management of patients who have failed prior endoscopic or surgical treatments [14], even if with only partial and not durable effects [9].

## Pneumatic balloon dilation

PD aims at disrupting the LES by a forceful stretching of the muscle fibers with an air filled balloon. The procedure is easy, reproducible, inexpensive and effective in long-term follow-up, when performed by using precise standards and in properly selected patients [15–21].

The procedure has become safer and easier after the adoption of non-compliant polyethylene balloons [21,22]. The major advantage of these balloons is that they are can be inflated only until a certain, pre-fixed diameter (more common sizes are 30, 35 and 40 mm) and that this diameter does not change by increasing the inflating pressure. This is extremely important to prevent perforation.

The technique of dilation is the following [1]. The patients are kept on a liquid diet for several days and fast completely for 12–24 h before the procedure (especially patients with

**Table 1. Principal features of each treatment of achalasia, including strengths and weaknesses, indication and response rate.**

| Treatment | Strengths | Weakness | Indications | Response rate |
|---|---|---|---|---|
| Medical therapy | Inexpensive<br>Very low complication rate | Incomplete efficacy<br>Efficacy quickly decreases with time<br>Side effects (head ache, pedal edema) | Elderly and/or patients with high surgical risk<br>Bridge-to-surgery<br>Esophageal pain or spastic disorders | Incomplete and temporary |
| Botulinum toxin injection (BTI) | Inexpensive<br>Low complication rate<br>No need for anesthesia<br>Effective at short term | Efficacy quickly decreases with time<br>Need of repeated treatments<br>Loss of efficacy in case of repeated treatments | Elderly and/or patients with high surgical risk<br>Bridge-to-surgery<br>Esophageal pain and spastic disorders | 79% at 1 months<br>53% at 6 months<br>41% at 12 months |
| Pneumatic balloon dilation (PD) | Technically easy procedure<br>Not expensive<br>Low complication rate<br>Reproducible<br>Efficacy at long-term follow-up<br>Feasible after failed POEM or LHM | Need of repeated treatments (graded dilator approach)<br>Less effective in young male patients<br>Reduced efficacy in type III achalasia | Elderly<br>Fist-line therapy for type I and type II achalasia<br>Bridge-to-surgery<br>Failure of LHM or POEM<br>Young patients who cannot undergo POEM or LHM | 30–93% at 10years |
| Per-oral endoscopic myotomy (POEM) | Theoretical long-term efficacy<br>No need for operating room<br>Reproducible<br>Low complication rate<br>Feasible after failed LHM or PD<br>Feasible in children<br>Possibility of very long myotomy | Need of oro-tracheal intubation<br>Lack of long-term validation<br>Need of expert endoscopists and referral centers<br>Possible high incidence of GERD | Any type of achalasia<br>ASA I-II-III<br>Sigmoid achalasia<br>Pediatric achalasia (with some concerns about the risk of GERD)<br>Treatment of spastic motility disorders | >93% at 12 months<br>Efficacy may decrease with time |
| Esophageal stenting (SEMS) | Easy and reproducible procedure<br>High success rate (reported in some series) | Moderate risk of complications (pain, GERD, bleeding and stent migration)<br>Clinical success decreases with time<br>Lack of long-term validation and need for additional multicenter studies | Elderly<br>Patients with severe comorbidities | >80% at 12 months<br>Efficacy substantially decreases with time |
| Laparoscopic Heller myotomy + Dor procedure (LHM) | Long-term efficacy<br>Feasible after PD and BTI<br>Anti-reflux procedure | More expensive than endoscopy<br>Longer hospitalization than endoscopy<br>Best results in referral centers with expert surgeons | Young patients<br>Any type of achalasia<br>ASA I or II | 80–90% at 15 years follow up |
| Esophagectomy | Ultimate solution after failure of alternative treatments | Major surgical operation<br>Should be performed only in referral centers<br>High mortality (5–10%) and morbidity rate (>50%) | Extreme esophageal dilatation unresponsive to endoscopic treatment or LHM<br>End-stage disease<br>Pre-neoplastic lesions | 75–95% |

sigmoid esophagus). PD is usually done as an outpatient procedure, even if preoperative hospitalization may be required in some elderly and dehydrated patients. PD is usually performed under fluoroscopy. The balloons cannot pass through the operating channel of the endoscope, and fluoroscopy is very useful to precisely place the balloon across the EGJ, and to maintain it in the correct position during inflation. When fluoroscopy is not available, or in case of extreme need, experts can perform PD under endoscopic control [23]. An EGD is carried out to rule out esophagitis or other lesions. The balloon is then pushed over a stiff guide-wire, previously placed under endoscopic control, and positioned across the EGJ (radiopaque markers on the balloon ease its positioning). According to a widely accepted graded dilation protocol [1], the smallest balloon diameter (30 mm) is generally chosen for the first dilation. Larger balloons can be used for the following dilations. The balloon is distended with air, for a more gradual dilation (air is compressible, liquids are not!). The key of the procedure is to maintain the waist caused by the non-relaxing LES at the mid part of the balloon. The device is distended slowly, and with relatively low pressures, until the waist on the balloon is flattened: 5–10 psi is usually enough for this purpose. The balloon is kept in place inflated for a variable time (15–60 s). It might be useful to deflate the balloon after the first dilation, reposition the balloon and then inflate it again, to be sure to have completely stretched the LES fibers. Immediately after dilation, an EGD should be performed, to rule out perforation. If no complications are suspected at EGD, and the patient has no complaints, an x-ray contrast study with Gastrografin® is usually not necessary. After the procedure, patients should be observed for 2–6 h. Hence they are allowed to drink and have a soft diet.

The graded dilation approach is now preferred by the vast majority of the experts and it is associated with substantial symptoms improvement in 50–93% of cases [15]. When a 'single dilation' approach is performed, the overall success rate is lower, especially in the long term [21]. For initial dilation, a 30 mm balloon is recommended for most patients followed by symptoms assessment, HRM and/or barium study in 4–6 weeks. If the patient is still symptomatic, the next size dilator should be used (35 mm) and then again, if necessary, also the 40 mm dilator. Initial dilation with a 30 mm balloon is also recommended because it reduces the risk of perforation [5], compared to the initial use of a larger balloon.

However, the above reported description is just a general rule. Different centers adopt different protocols for the dilation [21]. Some do a single dilation and redo the procedure only in case of symptoms recurrence; others repeat the dilation after some weeks, regardless of the clinical conditions [21]; serial progressive dilations over several days until LES pressure is below 10–15 mmHg are also performed [16,24]. Some authors increase the diameter of the balloon for the second dilation, some others do not [21]. The duration of inflation (6 s to 5 min) and the pressure of the balloon (6–15 psi) also vary at different centers [21]. The variability of the dilation protocols might be responsible for the different results published in the literature.

In a review by Richter *et al.* [25] that included 1144 patients, overall good-to-excellent results have been reported in about 78% of patients with a follow-up of 37 months. Clinical response improved with increasing size of the balloon and was 74, 86 and 90% with the 30, 35 and 40 mm balloons, respectively.

In another recent meta-analysis of 29 studies, Katzka *et al.* [21] reported that the response for a single dilation session was 66% at 1 year, 50 and 25% at 5 and 10 years, respectively. Multiple dilations during the initial treatment improved the efficacy of PD. Furthermore, when the Rigiflex balloon (Boston Scientific, Natick MA, USA) was used, the overall 1-year efficacy was 88%, gradually declining with time to 70 and 29% after 5 and 10 years, respectively.

Recurrences may occur at long-term follow-up. However, the vast majority of patients with symptoms recurrence can be easily managed with repeated dilations [24,26]. In a large study by Zerbib *et al.* [26], the probability to be in remission at 5 and 10 years after the initial clinical response was 67 and 50%, respectively. The vast majority of patients with recurrences underwent additional PD, and among this group of patients, the probability of being in remission after repeated PD at 5 and 10 year was 96.8 and 93.4%, respectively.

Studies have been done to select ideal candidates for PD. According to a variety of studies, factor predictors of favorable clinical outcome after PD are female gender [19,27–29], older age (>40–45 years) [16,24,27–29], esophageal diameter >3 cm [28], LES pressure after dilation <10 mmHg [16,24,27,30] and type II achalasia at HRM [3,31,32].

Complications after PD are rare. The most fearful and frequent is esophageal perforation. Overall incidence of perforations is 2%, but at least 50% of patients with perforations are managed conservatively [21]. Usually perforations occur during the first dilation [15], and perforation rate seems to be higher when PD is performed with a 35 mm balloon [5].

Another important issue that needs to be addressed is the incidence of GERD after PD. Little data, with a short follow-up, are available about iatrogenic GERD prevalence and management. Furthermore, in most studies, only symptoms have been evaluated and not pH-monitoring data. When pH-monitoring study has been performed, incidence of altered esophageal acid exposure has been documented in 11–31% of patients. Only a minority of patients complained of GERD symptoms [5,22,33–35]. In a recent study by Bravi *et al.* [35] on 69 patients treated with PD, 28% had GERD symptoms (but only 11% had continuous or severe heartburn and required prolonged PPI therapy), 7% of patients had esophagitis and 28% altered esophageal acid exposure at pH-metry.

Over time, the proportion of patients remaining in remission after PD decreases. If some patients prefer to undergo repeated dilations, some others prefer a more definitive operation, especially in case of early failures. After PD, surgery or POEM can be performed without major difficulties, even if some authors

reported some problems during LHM caused by fibrosis in the muscular layer and submucosa [10].

At the same time, PD represents the first-line salvage technique after a failed POEM or LHM. No severe complications are usually reported if PD is performed after a failed LHM [1,36]. However, the management of treatment failures is really challenging, and a multimodality approach should be offered to the patients, in referral centers.

## Peroral endoscopic myotomy

POEM is an endoscopic procedure, recently developed for the treatment of esophageal motility disorders, which theoretically combines the long-term benefits of a surgical myotomy with the advantages of a trans-oral, minimally invasive approach. An endoscopic myotomy was first described in the 1980s by Ortega *et al.* [37], who cut the circular muscle bundles of the LES directly through the mucosa. This method never gained wide acceptance because of concerns of potential mediastinal contamination when injuring the mucosa [38].

After the advances of endoscopic submucosal dissection (for the management of early neoplasms), and the development of natural orifice transluminal endoscopic surgery (NOTES), a new approach to endoscopic myotomy was proposed and used first, on the animal model, by Pasricha [38], and then, on humans, by Inoue [7]. The current POEM technique includes the following steps: incision of the esophageal mucosa, approximately 13 cm above the EGJ; submucosal dissection and creation of a tunnel into the esophageal wall; the submucosal tunnel is extended for 3 cm beyond the EGJ into the gastric wall; myotomy, preferably including the circular bundles of the muscularis propria of the distal esophagus and cardia; closure of the mucosal defect with clips (Figure 1). The submucosal tunnel prevents a direct communication between the esophageal lumen and the mediastinum and minimizes the risk of mediastinal contamination and infections.

In the initial report in humans by Inoue *et al* [7], the completion of endoscopic myotomy was achieved in all the patients (n = 17), and no serious complication occurred. During a 5-month follow-up, significant symptom improvement was registered (dysphagia symptom score decreased from 10 to 1.3) along with a reduction of the mean LES pressure (from 54.4. to 19.9 mmHg).

Theoretically, any patient with achalasia can be a candidate for POEM. The procedure is technically easier when the esophagus is not dilated, even if experienced endoscopists can manage also patients with very dilated and sigmoid esophagus [39]. The procedure requires oro-tracheal intubation, and, in expert hands, requires about 40–70 min to be completed.

Many series including a relatively large number of patients have been published. These studies showed clinical success in 89–100% of cases [11,40–51]. The shortcoming of these reports is that the follow-up is relatively short, and the vast majority of the studies are single center. Achalasia is a chronic illness, and the efficacy of any kind of treatment should be especially evaluated at long term. Furthermore, most of the POEM studies do not report the actual survival (i.e., absence of dysphagia) of the patients at a given intervals (6 months, 1 year, 18 months and so on) and, as a consequence, long-term data on POEM are difficult to analyze.

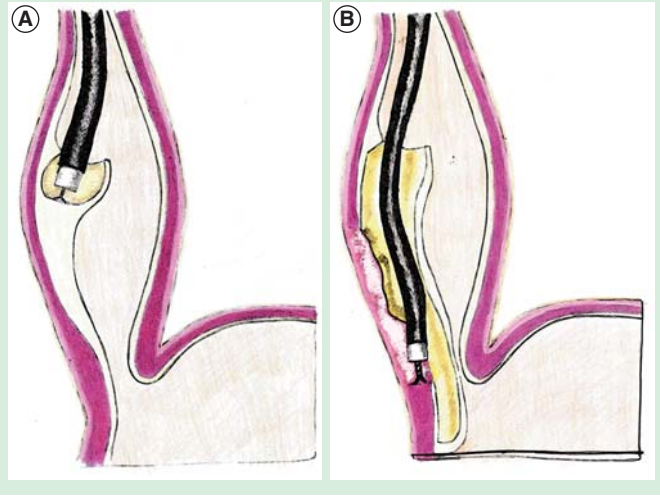


**Figure 1. Peroral endoscopic myotomy. (A)** Entry to submucosal space. After submucosal injection, a small longitudinal mucosal incision is made at approximately 10–13 cm proximal to the esophago-gastric junction. A long submucosal tunnel is created. **(B)** Endoscopic myotomy of inner circular muscle bundles starts at 3 cm distal to the mucosal entry point and is carried out until 2–3 cm distal to the esophago-gastric junction.

One of the few multicenter studies that reports on the mid-term results of POEM has been published by Von Renteln *et al.* [48]. It shows a gradual decrease of the success of POEM along time, with results similar to LHM. In this study, clinical success rate decreased from 97.1% at 3 months to 88.5% and 82.4% at the 6-month and 12-month follow-up. GERD-rate after POEM was 33, 30 and 37% at the 3-month, 6-month and 12-month follow-up, respectively (Table 2).

Overall, the safety profile of POEM is excellent. Very few mild complications have been reported in published series. Severe complications are rare and include few cases of full-thickness esophageal perforation and delayed bleeding [11,40–52].

Very common adverse events during the procedure are transient and self-limiting pneumoperitoneum, pneumomediastinum and cervical emphysema [11,40–52]. However, these events do not substantially modify the postoperative course and should not be considered as complications. Only in two Chinese series [40,52], a variety of severe 'gas-related' complications have been reported, including pneumothorax, thoracic effusions, lung atelectasis and severe bleeding. However, these complications were likely caused by the insufflation of room air during the procedure, instead of carbon dioxide.

The outcomes of 100 patients with a mean follow-up of 16 months were reported by the group of Swanstrom [45]. Seventy-five patients had achalasia, 12 nutcracker esophagus,

5 diffuse esophageal spasm and 8 isolated hypertensive non-relaxing LES. POEM was completed in all the cases. The overall morbidity was 6%: all complications were treated endoscopically or with conservative management without additional consequences. Dysphagia was improved in 97% of patients with a complete resolution obtained in 89%. Complete dysphagia relief was higher for achalasia patients (97.8%) versus non-achalasia patients (70.8%). Four patients had recurrent dysphagia. Two non-achalasia patients underwent subsequent LHM without substantial benefits, and two achalasia patients improved following serial endoscopic dilations. Abnormal acid exposure was present on postoperative testing in 38% of patients (26/68). Of these, 14 were asymptomatic.

A group from Chicago (USA) [46] recently published on 41 patients with achalasia treated with POEM and followed for a mean of 15 months. One (2%) major complication, a contained leak at the EGJ requiring re-operation, and seven (17%) minor complications occurred in this series. Clinical success was recorded in 92% of patients. Fifteen percent of patients had GERD symptoms during the follow-up. pH monitoring studies showed altered esophageal acid exposure in 31% of patients (4 out of 13). However, postoperative upper endoscopy revealed esophagitis in 59% of patients.

Ling *et al.* [44] published a series of 87 patients with achalasia treated with POEM and followed for a minimum of 1 year. Clinical success was achieved in 97.7% of patients. The few complications included mucosal injuries in 2% of patients and pneumothorax in 1%. Esophagitis was diagnosed in five patients, and other four patients had symptoms of GERD and were successfully treated with PPIs.

In a series of our first 100 patients [11], the procedure was technically feasible in 94% of cases, with a mean operative time of 83 min (49–140 min). No complications occurred in these patients. A mean follow-up of 11 months was available for 92 patients. Clinical success was reported in 94.5% of patients. 24-h pH monitoring documented altered esophageal acid exposure in 53.4% of patients. However, only a minority of patients had GERD symptoms (24.3%) or esophagitis (27.4%), and all these patients were successfully treated with PPIs.

In all of the aforementioned studies, the postoperative LES pressure was accounted as a parameter of treatment success together with symptom resolution. However, interesting data emerged from a recent study [53] that investigated whether assessment of the distensibility of the EGJ is a better parameter than LES pressure for evaluating the efficacy of the treatment. In this study, such an evaluation was made in patients treated with PD or LHM. The results showed that EGJ distensibility correlates well with esophageal emptying and, most importantly, with symptoms. In line with those observations, the authors of the study suggest that methods that determine the EGJ distensibility should be used to evaluate treatment success and the need of further therapy. Although HRM is the recognized standard diagnostic tool for achalasia, the effect of the therapy should be evaluated with timed barium esophagogram and/or with EndoFLIP. More recently, EndoFLIP has been also used to intraoperatively evaluate the distensibility of the EGJ during the POEM procedure [54–56].

Previous management of achalasia, including BTI, PD or LHM, does not preclude POEM [11–13,57–60]. In a series published by Orenstein *et al.* [13], 40 patients received a POEM procedure, and 40% of them had had at least one prior endoscopic or surgical procedure, including nine BTI, seven PD, three both BTI and PD and three prior LHM (two with Dor fundoplication). Mean operative time, intraoperative adverse events and success rate were not substantially dissimilar in the two groups.

POEM has shown a potential role in the management of patients with refractory symptoms despite previous HM. However, some experts recommend an attempt at PD before POEM [58].

Previous surgical treatment causes surrounding adhesions, which increase the risk of failure for laparoscopic re-myotomy. The results of published studies support the role of POEM in the case of failed HM [13,58,60]. POEM can be safely performed in these patients, since the whole procedure is intraluminal and the site of the submucosal tunneling may be directed on an unaffected part of the esophagus.

Onimaru reported on 10 patients with a failed HM, who underwent POEM with clinical success, after the failure of PD [58]. In a series by Zhou *et al.* [60], 12 patients with a failed HM underwent POEM, and clinical success was achieved in 91% of patients. There are also reports of patients treated with POEM after gastric resection [61].

POEM can be easily performed on children older than 3 years, using standard endoscopes and ancillaries [40,62,63]. The largest series has been published by Chen *et al* [40], who recently reported on 27 pediatric patients. POEM was successful in 26 cases. No serious adverse events occurred and, during a mean follow-up period of 2 years, success was achieved in all patients. POEM is not substantially difficult when performed on children: the esophagus is shorter, the esophageal submucosa less fibrotic than in adults and the procedure is usually more rapid. Furthermore, because of the dilatation of the esophagus caused by the disease, no specific modifications to the technique are necessary.

One of the major advantages of POEM compared to surgery or to the other therapeutic options is that the length of the myotomy can be very easily customized according to the patient's needs. This is particularly useful for the treatment of patients with type III achalasia, where PD and LHM are poorly effective at long term [3,64], and where a longer myotomy on the esophageal site may be indicated to relieve dysphagia and pain. However, only scanty data are available on the efficacy of POEM on type III achalasia and other spastic motility disorders [65,66].

POEM is not associated with any anti-reflux procedure, and this represents one of the main limits. When GERD has been evaluated using pH-monitoring studies, a high prevalence of

**Table 2. Outcomes of recently published POEM series.**

| Author (year) | City, Country | No. of cases | Technical success | Previous treatment | Clinical success | Mild AEs and gas-related AEs | Complications | Altered esophageal pH-metry | Esophagitis | GERD symptoms | Follow-up (months) | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inoue *et al.* (2010) | Yokohama, Japan | 17 | 100% | None | 100% (17/17) | 6% (1/17) | None | n/a | 6% (1/17) | 6% (1/17) | 5 | [7] |
| Chiu *et al.* (2013) | Honk Kong, China | 16 | 100% | 2 HM | 100% (16/16) | 19% (3/16) | None | 20% (3/15) | n/a | 6% (1/16) | 6 | [67] |
| Lee *et al.* (2013) | Seoul, Korea | 13 | 100% | 3 PD – 2 BTI 1 HM | 100% (13/13) | n/a | none | n/a | n/a | n/a | 7 | [42] |
| Von Renteln *et al.* (2013) | Multicenter | 70 | 100% | 24 unknown | 82% (42/51)[#] | 11% (8/70) | 3% (2/70) | n/a | 42% (29/70) | 33% (23/70) | 10 | [48] |
| Verlaan *et al.* (2013) | Amsterdam, The Netherlands | 10 | 100% | 2 PD – 1 SEMS | 100% (10/10) | none | none | n/a | 60% (6/10) | 30% (3/10) | 3 | [50] |
| Li *et al.* (2013) | Shanghai, China | 238 | 98% (234/238) | 53 PD – 5 SEMS 5 BTI – 14 Other 14 HM – 1 POEM | 90% (210/234) | 17%[§] (40/234) | 0.8% (2/234) | n/a | 8.5% (20/234) | 17% (39/234) | 8 | [43] |
| Minami *et al.* (2014) | Nagasaki, Japan | 28 | 100% | 10 PD – 1 HM | 100% (28/28) | 3% (1/28) | 7% (2/28) | n/a | 39% (11/28) | 21% (6/28) | 16 | [47] |
| Stavropoulos *et al.* (2014)[¶] | New York, USA | 100 | 100% | 20 BTI – 11 PD 7 HM | 96% (51/53)[#] | 25% | none | 33% (17/52) | 32% (17/53) | 16% | 13 | [49] |
| Ling *et al.* (2014) | Nanjing, China | 87 | 100% | None | 95% (83/87) | 14% (12/87) | 2% (2/87) | n/a | 6% (5/87) | 10% (9/87) | 14 | [44] |
| Teitelbaum *et al.* (2014) | Chicago, USA | 41 | 100% | 4 (10%) | 92% (38/41) | 58% (24/41) | 2% (1/41) | 31% (4/13) | 59% (13/22) | 15% (6/41) | 15 | [46] |
| Familiari *et al.* (2014) | Rome, Italy | 100 | 94% (94/100) | 5 BTI – 19 PD | 94% (87/92)[††] | 50% (47/94) | none | 53% (39/73) | 27% (20/73) | 24% (17/73) | 11 | [11] |
| Sharata *et al.* (2015)[‡] | Portland, USA | 100 | 100% | 20 BTI – 10 PD 5 HM | 97% (97/100) | 5% (5/100) | 1% (1/100) | 38% (26/68) | 27% (20/73) | 8% (7/81) | 16 | [45] |
| Chen *et al.* (2015)[†] | Shanghai, China | 27 | 96% (26/27) | 1 BTI – 5 PD 1 SEMS | 100% (26/26) | 19%[§] (5/26) | none | n/a | 11.5% (3/26) | 15% (4/26) | 25 | [40] |
| **Total** | | **847** | **99% (836/847)** | | **93% (718/768)** | **21% (171/813)** | **1.2% (10/843)** | **40% (89/221)** | **21% (145/693)** | **17% (116/683)** | **Mean 12 months** | |

[†]Series including only pediatric patients.
[‡]25% of included patients have spastic motility disorders.
[§]Gas-related adverse events caused by the use or room air during POEM instead of carbon dioxide were excluded.
[¶]Data published in abstract form and presented at Digestive Disease Week 2014.
[#]Data from 12-month follow-up.
[††]Two out of 94 patients effectively treated were lost to follow-up.
AE: Adverse events; BTI: Botulinum toxin injection; PD: Pneumatic balloon dilatation; HM: Heller myotomy; SEMS: Self-expanding metal stent; GERD: Gastroesophageal reflux disease.

altered esophageal acid exposure, varying between 20 and 53%, have been documented [11,45,46,67]. The prevalence of esophagitis at EGD was lower, between 8.5 and 42% [11,43,45,47,48,67]. Heartburn is usually complained by 15–20% of the patients [11,43,45–48,67]. Even if all the patients with GERD and esophagitis in the published series have been successfully treated with PPIs, GERD can be responsible for the onset of peptic strictures or Barrett's esophagus.

The role of POEM in the management of esophageal achalasia is really promising but still not well validated and defined. A close follow-up is thus necessary for all the patients, to evaluate the long-term results.

## Esophageal stenting

The role of Self-Expanding Metal Stent (SEMS) for the treatment of achalasia is still not well defined. Over the last 15 years, some studies evaluated the efficacy and safety of the procedure [68–71], and some comparative trials versus PD are also available [72–74]. A variety of stent models have been used in the published series: differences included mesh design, presence of a covering and diameter. However, the published results are excellent, usually superior to the results of PD, with a limited complication rate. Some authors advocate that the explanations for these positive results may lie in the slow symmetrical pressure placed on the LES over a prolonged period of time, leading to a more complete disruption of the LES.

Three Chinese studies including a large number of patients have been recently published [68,70,71]. Zhao *et al.* [71] reported on 75 patients treated with a 30 mm partially covered SEMS for 3–7 days. All the patients were treated successfully, and during the very long follow-up (up to 13 years!) the overall remission rate remained very high: 100 and 83% at 5 and 10 years, respectively. Complications included 5.3% of SEMS migration, pain (38%), GERD (20%) and bleeding (12%).

Cheng *et al.* [70] prospectively evaluated the role of the SEMS diameter on the clinical efficacy and complication rate. Ninety patients were treated by a temporary SEMS for 4–5 days (30 patients with a 20 mm SEMS, 30 patients with a 25 mm and 30 with a 30 mm SEMS). Stent placement was successful in all patients. Although chest pain occurrence was high (40%), stent migration was lower (7%) in the 30 mm-SEMS group compared to the 25 mm-SEMS (13%) and 20 mm-SEMS group (27%). At the same time, during a mean 7-year follow-up, the treatment failure rate was lower in the 30 mm SEMS group (13%) than in the 20 mm SEMS groups (53%) and 25 mm-SEMS group (27%).

Zeng *et al.* [68] evaluated fully covered SEMS (20 and 25 mm in diameter) in 59 patients. SEMS were left for 30 days. The cumulative clinical remission rates at 6, 12, 18, 24, 30 and 36 months after stent removal were 90.9, 81.8, 76.4, 69.1, 65.5 and 49.1%, respectively. Twelve patients (25.5%) complained of chest pain and 10.6% had heartburn. SEMS migrated in 8.5% of patients.

Some small case series have been published also by few Western centers [69,75]. In 2001, De Palma *et al.* [75] reported on eight patients treated with Nitinol coil stents and covered Ultraflex stents. Previous myotomy and/or PD or BTI had failed in these patients. Complications were seen in 62% of patients, and including chest pain, GERD and SEMS migration. One patient underwent surgery for stent impaction in the colon. Another study from Italy [69] reported on seven patients with achalasia treated with a partially covered SEMS. The SEMS were removed after 6 days. No complications occurred, and during a mean follow-up of 19 months, clinical success was reported in 70% of patients, whereas the other patients experienced significant improvement of dysphagia.

At least three Chinese series compared the efficacy and safety of esophageal SEMS versus PD in a large number of patients [72–74]. The overall results of all these series demonstrated a higher clinical remission rate with a 30 mm-SEMS compared to PD (83–89% vs 0–42%, respectively).

SEMS placement is extremely appealing, being simple and safe. However, enthusiasm should be tempered by reported case series not using validated symptom questionnaires, using non-traditional measurements of post-procedure LES pressure, and not assessing esophageal emptying. The overall success is likely similar to that of a single-balloon pneumatic dilation, further tempered by a high reported rate of stent migration in many series [76].

Additional studies performed also in Western centers are necessary to definitely assess the efficacy and critically evaluate the role of SEMS in the management of achalasia.

## Laparoscopic Heller myotomy

Surgical extramucosal cardiomyotomy was initially described by Ernest Heller in 1914 and, with some modifications, has been the only effective treatment of achalasia over more than 50 years [77].

With the evolution of therapeutic flexible endoscopy during the 1980s, PD gained wide consensus and was often proposed as a first-line treatment of achalasia. Endoscopy is less invasive and expensive than thoracotomy or laparotomy. However, after the great initial enthusiasm, overall long-term results favored again surgery especially because of the development and diffusion of minimally invasive surgery [6,77]. Some clinical trials demonstrated that symptoms improvement was significantly higher with a laparoscopic approach than with a thoracoscopic approach. In a large review by Campos *et al.* [6] clinical success was achieved in 89% of patients treated with laparoscopy and 78% of patients who underwent thoracoscopy ($p < 0.05$) [6].

Some authors have reported better results when the myotomy is extended for 3 cm beyond the EGJ on the gastric wall, instead of 1–1.5 cm. The sling fibers and clasp fibers on the gastric wall work in synergy with the LES and should be cut to favor the esophageal emptying [78,79].

A high incidence of iatrogenic GERD is reported after LHM without any anti-reflux procedure (up to 60%) [6,80]. The need for an anti-reflux fundoplication has been the object of debate for years, but it is now recommended by the vast majority of experts and by guidelines [1]. In a large meta-analysis published

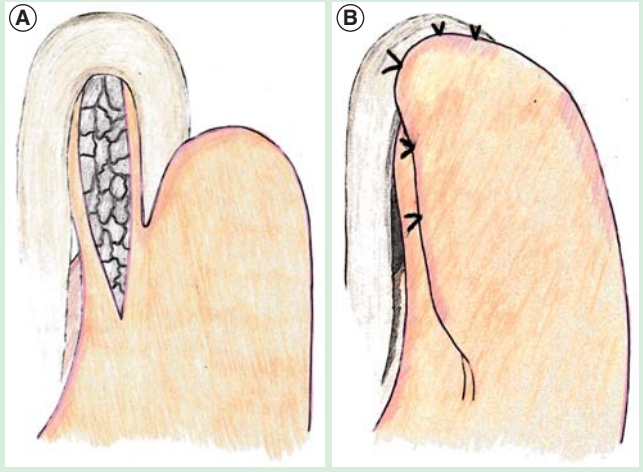


**Figure 2. Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). (A)** Laparoscopic myotomy is approximately 8 cm long, extending onto the esophageal wall for about 6 cm above the esophago-gastric junction and distally for about 2 to 2.5 cm onto the gastric wall. **(B)** Anterior partial fundoplication in the context of a Heller myotomy. The gastric fundus is mobilized, folded over the myotomy area and fixed with stitches to the esophageal wall and the left pillar of the diaphragm.

in 2009, on a total of 3086 patients, Campos *et al.* [6] demonstrated similar clinical success but a significant reduction of GERD symptoms and esophagitis (31 vs 9%, $p = 0.001$) when an anti-reflux wrap was associated to the myotomy. Nevertheless, in some series, even if a fundoplication was added to the myotomy, a high prevalence of altered esophageal acid exposure at pH-monitoring studies can be observed after LHM (between 21 and 54%) [5,78,81,82]. Other authors reported a rate of altered esophageal acid exposure lower than 6% [6,36].

The type of fundoplication has been also a matter of debate. A partial wrap is usually preferred because the esophagus of patients with achalasia has no peristalsis, and a Nissen fundoplication could impede esophageal emptying [83]. A randomized trial compared LHM plus Dor and LHM plus Nissen fundoplication [84]. At long-term follow-up, the GERD rate was similar in the two groups. However, a statistically significant difference in dysphagia rates was noted (2.8 vs 15%, for Dor and Nissen fundoplication, respectively; $p < 0.001$). Other studies, including also a randomized controlled trial, compared anterior (Dor) and posterior (Toupet) partial fundoplication and showed similar results in terms of symptoms improvement and GERD rate [78,81].

Experts prefer Dor fundoplication to Toupet procedure also for other reasons. First, a Dor fundoplication is technically less demanding, because there is no need to dissect the posterior esophageal wall. Second, the anterior partial wrap covers the myotomy area and may prevent complications caused by microperforations that can accidentally occur during the myotomy (Figure 2) [36,83].

In expert hands, LHM with anti-reflux procedure have an average success rate as high as 90% [1,5,6]. Furthermore, the safety profile of the procedure is excellent. Overall procedure-related mortality is less than 0.1%, and the vast majority of the reported complications are mucosal gastric or esophageal perforations which are usually immediately recognized and repaired without consequences [6].

Zaninotto *et al.* [36] have recently published the results of a large series of 407 patients with achalasia who underwent LHM with Dor fundoplication during a 15-year period. Relief of dysphagia was reported in 90% of patients. Treatment failure occurred in 10% of patients, in 64% of the cases during the first 12 months. Early treatment failures underwent PD with relief of symptoms in 75% of cases. Postoperative GERD was detected in only 6% of the 260 patients evaluated with a 24-h pH monitoring, and mucosal erosions were found in 20% of the GERD patients. Esophageal mucosal perforations occurred in 3.9% of patients and were detected and repaired intraoperatively in 88%. No correlation was reported between perforation and previous endoscopic therapies. This is in contrast with the findings of Smith *et al.* [10] who reported that previous endoscopic therapies (PD or BTI) could increase intraoperative and postoperative complications as perforation (17%) or incomplete myotomy due to fibrosis.

As for PD, the preoperative manometric pattern at HRM affects clinical success rates after HM. Patients with achalasia type II have the best outcome compared to patients with type I or type III achalasia [3,64].

Recent improvements in the laparoscopic surgical technique are robotic surgery and single-site laparoscopic surgery. There are still some concerns about the use of an expensive robotic surgery for a well-standardized and relatively easy operation. However, Horgan *et al.* [85] in a retrospective multicenter study compared standard LHM with robotic HM and showed that the incidence of perforation was 0% in the robotic group versus 16% in the standard LHM group. No substantial advantages were reported in terms of clinical outcomes. In 2011, Barry *et al.* [86] also reported on 66 patients which underwent single-site LHM with anterior partial fundoplication. All the procedures were completed successfully, without major adverse events, even if additional ports or incisions were required in 16% of patients. Additional confirmation on the potential benefits of these approaches is awaited.

## Esophagectomy for end-stage disease

Esophagectomy is rarely necessary for the treatment of achalasia. The main indications are abnormal esophageal dilation and sigmoid esophagus, associated with food retention and severe dysphagia or regurgitation, unresponsive to standard surgical or endoscopic treatments. The presence of pre-neoplastic esophageal lesions may also justify esophageal resection. End-stage diseases develop in 2–5% of patients [87].

Some experts recommend esophagectomy only in those patients who have a tortuous, sigmoid-shaped mega-esophagus, stating that the tortuosity will interfere with esophageal emptying even after HM. Patients with a dilated but straight esophagus may better benefit from HM as a first choice [88].

Esophagectomy is a major surgical operation that should be performed in referral centers. Mortality rate is 5–10% and morbidity rate up to 50%. The risk of anastomotic leaks is about 10–20% [89]. Furthermore, esophagectomy in end-stage achalasia patients is technically more difficult than esophagectomy for cancer, because of anatomical alterations due to the megaesophagus and a higher risk of intraoperative bleeding [88,89].

The ideal reconstruction after esophagectomy is still debated. Some prefer esophago-gastric anastomosis and some others colonic interposition [87,89].

## Expert commentary

Current scientific evidences and guidelines suggest that LHM, associated with an anti-reflux procedure, is still the gold standard for the treatment of achalasia, especially in young patients, without comorbidities. Furthermore, surgery currently represents the ultimate solution, when other treatments fail.

However, when PD is performed according to well-defined protocols (repeated dilations and graded dilator approach), it offers certain benefits that should not be underrated. PD is fast and inexpensive; it is feasible in almost all patients and does not preclude a subsequent myotomy, surgical or endoscopic.

Several studies compared LHM to PD. Recently, a large multicenter study [5] demonstrated that, at 2-year follow-up, LHM and PD have substantially the same clinical efficacy and complication rate with a similar GERD prevalence. In contrast, a following network meta-analysis published by Schoenberg *et al.* [90] demonstrated that LHM have the same complication rate of PD, but higher efficacy at any follow-up.

Nevertheless, PD should probably be considered the first-line therapy for patients older than 45–50 years with a type I or type II achalasia. Furthermore, PD is a valuable treatment in case of failed surgery or POEM.

Medical therapy and BTI should be reserved to very selected patients, who are at high risk for any other therapy, or as a bridge-to-surgery.

Some studies that compared BTI to PD and to LHM are also available. In a recent review [91], there was no significant difference between PD and BTI in terms of symptomatic remission within 4 weeks of the initial intervention. However, after 6 months, PD was more effective than BTI (80 vs 52%). A large randomized controlled trial of BTI versus LHM concluded that after 6 months, the results of surgery in BTI are comparable, although symptom scores improve more after LHM. At long term, the probability of being symptom-free is definitely higher after surgery than after BTI (87.5 vs 34%) [92].

The role of SEMS in the management of achalasia is promising, but needs additional data.

POEM is a very attractive technique, but the results currently available do not permit a definitive evaluation of the procedure.

Prospective randomized comparative trials of POEM versus LHM or PD are still lacking. Only retrospective, comparative trials have been published. Bhayani *et al.* [93], from Portland (USA), compared the outcomes of 64 LHM with fundoplication and 37 POEM. Operative time and hospitalization were significantly higher for LHM. Complication rate and success rate at 6-month follow-up were substantially similar. Abnormal acid exposure at pH-monitoring was similar in the two groups (39% form POEMs and 32% for LHM). Ujiki *et al.* [94] reported on 18 patients treated with POEM and 21 who underwent LHM. In the short term, POEM resulted in similar relief of dysphagia with less postoperative pain and quicker return to normal activities. Hungness *et al.* [95] compared 18 patients treated with POEM and 55 treated with LHM. Operative time and estimated blood loss, myotomy length, complication rate and hospital stay were similar, as well as the 6-month success rate.

Concerns about post-POEM GERD are fully justified. However, some advantages of POEM are evident and cannot be ignored. The endoscopic myotomy is relatively easy, fast, does not require an operating room, or expensive ancillaries, and the costs of the procedure are lower than the cost of surgery. POEM can be performed also in patients after the failure of previous surgery or endoscopic therapies, or in small children. Furthermore, the trans-oral approach is definitely preferred by the patients. More importantly, the length of the myotomy can be customized on the base of the patient needs, or HRM findings: a long myotomy on the esophageal side can be very useful for patients with type III achalasia (these patients poorly respond to both LHM and PD) or with other esophageal spastic motility disorders. However, while waiting for the long-term results of the ongoing studies and for comparative trials versus PD and LHM, POEM should still be performed in few referral centers and in the setting of clinical trials.

## Five-year view

All advantages and disadvantages of the currently available strategies for the treatment of achalasia will be better clarified in the next future, including the additional potentialities of surgery (robotic surgery) and minimally invasive procedures.

In the next 5 years, the results of some randomized controlled trials which compare POEM versus PD or versus LHM will be available. Additional clarifications on the real risk of GERD after POEM will come. Endoscopic anti-reflux procedures might become available for patients with GERD symptoms or esophagitis, or maybe a new combined procedure (POEM with anti-reflux procedure) will be developed.

In the meanwhile, costs of robotic surgery will decrease, and the potentiality of such an approach for achalasia will be evaluated. Cost-efficacy analyses comparing LHM, robotic surgery and POEM are awaited.

The current treatments of achalasia only act on symptoms, but do not correct the underlying muscular abnormalities, and do not recover peristalsis. Disappearance of myenteric neurons seems to be the primary cause of achalasia. Future researches should focus on the potential role of immune-modulatory drugs to arrest and reverse the neurons loss and recover

motility. Furthermore, neural stem cell researches are ongoing and stem cell transplantation will undoubtedly provide new options for treatment of aganglionic gastrointestinal diseases, including achalasia. However, it is difficult that these researches will be translated into the clinical practice within the next 5 years.

Medical, endoscopic and surgical treatments should work in synergy for the benefits of every single patient. Different treatments offer specific advantages that should not be lost because of corporative interests. Management of rare disorders like achalasia will be probably centralized in referral centers, or at least a network of specialists should be created, to evaluate and decide the best management of every single patient.

**Financial & competing interests disclosure**

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

## Key issues

- Esophageal achalasia is due to loss of the ganglion cells in the myenteric plexus of the esophageal body and the lower esophageal sphincter (LES) that leads to progressive dysphagia and reduced esophageal emptying.
- No etiological therapies are available for achalasia. Current treatments aim at reducing the LES pressure and improve esophageal emptying.
- Nitrates and calcium channel blockers, taken 15–30 min before meals, can only partially reduce the LES pressure.
- Single injection of botulinum toxin is relatively effective at short term, but the efficacy decreases with time and patients may require additional treatments.
- Pneumatic dilation causes disruption of the LES fibers by a forceful stretching with an air-filled balloon. The procedure is easy, reproducible, not expensive and generally effective at mid-term follow-up, if performed by using certain standards and in properly selected patients. The 'graded dilator' approach is preferred to improve long-term outcomes and minimize complication rate.
- Peroral endoscopic myotomy, the archetype of submucosal endoscopy, theoretically combines long-term benefits of a surgical myotomy with a trans-oral, minimally invasive approach. The procedure still needs long-term evaluation and comparison with other therapeutic options.
- Laparoscopic Heller myotomy is still considered the gold standard treatment for achalasia. Better results are obtained when myotomy is extended for 3 cm on the gastric wall and when an anti-reflux partial fundoplication is added to the myotomy.
- Esophagectomy is used in cases of abnormal esophageal dilation associated with food retention and severe dysphagia or regurgitation, unresponsive to standard surgical or endoscopic treatments.

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•• **The history of achalasia and its treatment, from the origins to nowadays. A very nice lecture.**

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