Received: 4 January 2022 | Revised: 13 July 2022 | Accepted: 1 August 2022

DOI: 10.1111/nmo.14459

CLINICAL REVIEW

Neurogastroenterology & Motility NGM WILEY

Achalasia: Current therapeutic options

Sebastien Rolland[1] | William Paterson[2] | Robert Bechara[2]

[1]Division of Gastroenterology, Hôpital Maisonneuve-Rosemont and Université de Montreal, Montreal, Quebec, Canada

[2]Division of Gastroenterology and GI Diseases Research Unit, Queen's University, Kingston, Ontario, Canada

Correspondence
Robert Bechara, Division of Gastroenterology, Hotel Dieu Hospital, 166 Brock St., Kingston, ON K7L 5G2, Canada.
Email: robert.bechara@kingstonhsc.ca

Abstract

Achalasia is an esophageal motor disorder characterized by impaired relaxation of the lower esophageal sphincter (LES) and absent peristalsis in the smooth muscle esophageal body. As a result, patients typically experience dysphagia, regurgitation, chest pain, and weight loss. Over the past 10–15 years, there has been a resurgence of interest in the evaluation of therapies for achalasia. Unfortunately, little progress in the development of effective pharmacological treatments has been made. Botulinum toxin injection provides some relief of symptoms in many patients but requires periodic reinjection that may provide progressively less benefit over time. There are now three well-established, safe, and effective therapies for the treatment of achalasia: pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic myotomy (POEM) which can lead to marked symptom improvement in most patients. Each treatment has a specific constellation of risks, benefits, and recurrence rate. The first-line treatment used will depend on patient preference, achalasia subtype, and local expertise. The recent impressive advances in both the art and science of achalasia therapy are explored with a comprehensive review of the various treatment modalities and comparative controlled clinical trials. In addition, key technical pearls of the procedural treatments are demonstrated.

KEYWORDS
achalasia, botulinum toxin, laparoscopic Heller myotomy, peroral endoscopic myotomy, pneumatic dilation

1 | INTRODUCTION

Achalasia is an esophageal motor disorder characterized by impaired relaxation of the lower esophageal sphincter (LES) and absent peristalsis in the smooth muscle esophageal body. As a result, patients typically experience dysphagia, regurgitation, chest pain, and weight loss. Earlier studies estimated the incidence of achalasia at 0.03–1.63/100,000 persons per year and the prevalence from 1.8–12.6/100,000 persons per year.[1,2] However, recent studies suggests that the incidence and prevalence may be at least 2-fold greater than this,[3] perhaps related to increased recognition since the adoption of high-resolution manometry (HRM).

Three subtypes of achalasia have now been defined[4] (Figure 1). In all types, there is impaired relaxation of the LES. In type I achalasia, there is dilation of the esophagus and virtually no pressure generation in the esophageal body during swallowing. In Type II, the esophagus tends to be less dilated and swallows result in pan-esophageal pressurization (common cavity phenomenon), which appears to be due to the bolus entering a closed cavity. This is the most common achalasia subtype. Type III achalasia (also known as vigorous achalasia) is characterized by significant "spastic" simultaneous contractions throughout the smooth muscle esophageal body.

Numerous pathophysiological studies support the hypothesis that the disease is due to loss of intrinsic inhibitory innervation, and in particular nitrergic neurons, within the myenteric plexus.[5] These intrinsic nitrergic neurons are responsible not only for the relaxation of the LES but also for the sequencing of peristaltic contractions in the smooth muscle esophagus. Interestingly, pharmacological studies suggest that this denervation in the myenteric plexus is limited to the inhibitory innervation, in that the excitatory cholinergic

responses appear intact.[6–8] Achalasia is characterized pathologically by a myenteric plexopathy, with infiltration of lymphocytes and associated destruction of the myenteric plexus neurons.[9–15] The degree of destruction seems to vary depending on the type and stage of achalasia,[12,14,15] with the degree of aganglianosis greatest in Type I achalasia and least in Type III.

The functional consequence of this pathophysiology is markedly impaired transit of food and fluid across the LES. Accordingly, a number of treatment strategies have evolved directed at ablating or at least lowering the resting LES pressure. This review will summarize currently available treatments for achalasia, focusing on recent developments, relative efficacy, and technical details of the different therapeutic approaches.

2 | TREATMENT MODALITIES

2.1 | Pharmacologic therapy

A drug taken just before meals that profoundly and selectively relaxes the LES during subsequent meal ingestion is arguably the most logical therapeutic approach to achalasia, in that it would alleviate dysphagia without causing permanent damage to the anti-reflux barrier. Unfortunately, no such ideal drug exists. A number of agents do relax the LES, but they are non-selective and generally not capable of consistently inducing sufficient relaxation without associated side effects. Furthermore, because their effect may be short-lived and time of onset variable, there can be a significant disconnect between the time of food ingestion and the peak relaxation effect of the drug. Accordingly, because of its long duration of action, the most popular pharmacologic approach to achalasia remains botulinum toxin injection into the LES circular smooth muscle. Nevertheless, a small subset of achalasia patients may benefit from smooth muscle relaxants administered orally or sublingually.

2.1.1 | Smooth muscle relaxants

Because of their ability to reduce resting LES pressures, nitrates, Ca++ channel blockers, anticholinergics, and phosphodiesterase inhibitors (sildenafil) have all been used in the treatment of achalasia, but outcome data from controlled clinical trials are limited (see Ref. [16]). Most reported experience is with nifedipine, either taken orally or sublingually prior to meals. In the placebo-controlled trials, resting LES pressure significantly declined post nifedipine ingestion when compared to placebo; however, improvement in symptoms versus placebo was inconsistent.[17,18]

Although less well-studied, it appears that isosorbide dinitrate may be more efficacious than nifedipine, in that it appears to

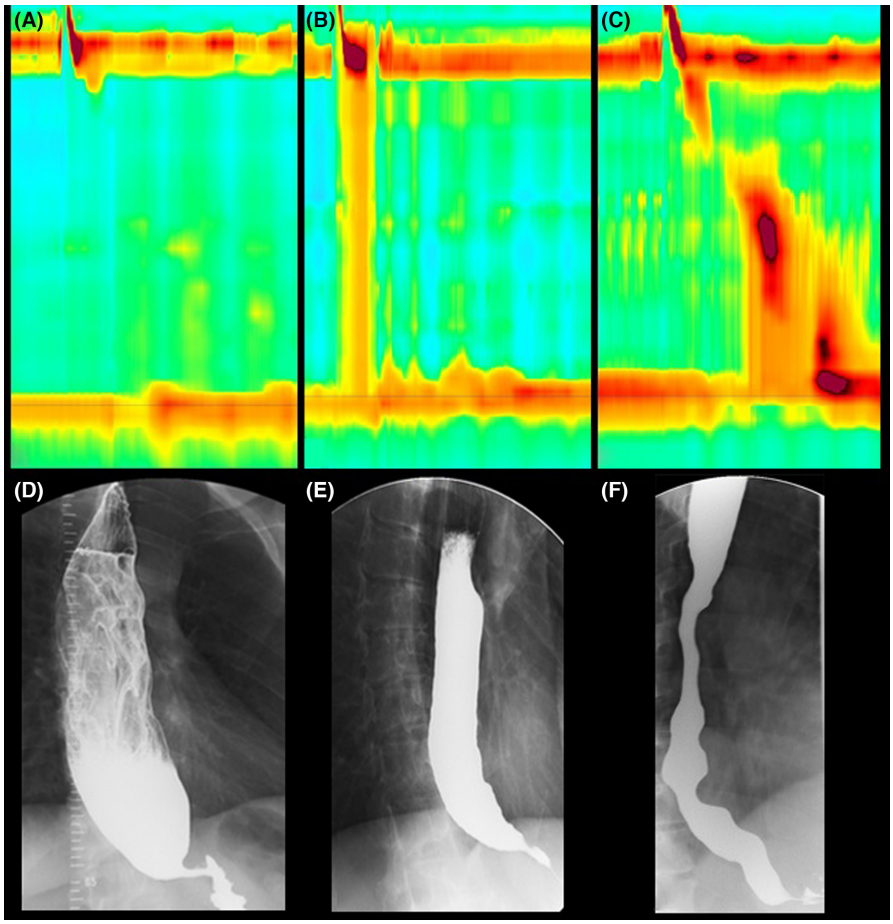

FIGURE 1 High-resolution manometry and Barium X-Ray features of Achalasia subtypes. All display impaired lower esophageal sphincter (LES) relaxation, usually characterized by a "bird-beak" narrowing at the LES radiographically (C, D). In type I, there is no significant pressure activity within the esophageal body in response to swallows, and the barium study typically reveals marked esophageal dilation (A, D). In type II, swallows result in panesophageal pressurization and the degree of esophageal dilation is less marked (B, E). In type III there are simultaneous contractions in the esophageal body that often produces a corkscrew effect on barium X-Ray (C, F).

produce better reduction in resting LES pressure and improvement in esophageal emptying.[19] Isosorbide dinitrate has also been shown to be efficacious in a placebo-controlled trial in patients with achalasia due to Chaga's disease.[20]

2.1.2 | Botulinum toxin

Given the selective loss of intrinsic inhibitory innervation in the LES and thus unopposed excitation, it was hypothesized that inhibiting the LES cholinergic excitation with botulinum toxin (BoTox) could lower resting LES pressure, with proof of concept demonstrated in a porcine model.[21] Subsequently, a small RCT in humans[22] in which four-quadrant injection of botulinum toxin (20 units in 1 ml per quadrant) was compared to equal volume saline injection demonstrated significant improvement in symptom scores, resting LES pressure, esophagogastric junction (EGJ) opening, and esophageal retention of barium that largely persisted at 6-month follow-up. Subsequently, a large number of observational studies and controlled clinical trials (see Ref. [23]) have confirmed the efficacy of this intervention.

A systemic review and meta-analysis of 22 uncontrolled studies in 730 patients revealed a success rate (based on Eckardt score declining to ≤3) of 77% (95% CI: 72%–81%), with follow-ups ranging from 1–6 months.[23] Unfortunately, symptom relapse in more than 60% of patients by 1 year, requiring retreatment.[24] It appears that the response rate with retreatment may decline.[25] Objective evidence of clinical efficacy is less impressive; however,[22,26,27] there is evidence that BoTox has greater efficacy in elderly patients and patients with type III achalasia,[28] which is important because the elderly often have co-morbidities that make more invasive treatment less desirable, and type III achalasia responds less well to pneumatic dilation and Heller myotomy.

The dose of BoTox injected has varied in different trials, but to date, there is no evidence that a total dose higher than 100 units injected into four quadrants of the LES produces better results. However, routine repeat injection of 100 U at 1 month appears to prolong response duration.[29] It is likely that the depth of injection is important (i.e submucosal vs. intramuscular injection). In a series of patients undergoing Heller myotomy following previous BoTox treatment, it was reported that there was usually a serosal reaction in patients who had responded well to BoTox treatment but not in those who had no symptomatic response.[30] It has been suggested that endoscopic ultrasound-guided injection[31] or injecting via a retroflexed view of the cardia[32] may afford more reliable delivery of BoTox into the LES muscle, but to date, there have been no studies demonstrating improved outcome using these methods as compared to standard technique. A video demonstrating practical details of the BoTox injection technique can be viewed here (Video S1).

Although quite safe, approximately 5% of patients experience chest or epigastric pain after the procedure, and there has been one reported death secondary to mediastinitis.[33]

2.2 | Pneumatic dilation

Pneumatic dilation (PD) aims to disrupt the LES muscularis propria fibers to alleviate the EGJ outflow obstruction, using an air-filled non-compliant polyethylene balloon. The most commonly used is the Rigiflex (Boston Scientific) balloon dilator that is available in three diameters: 30, 35, and 40 mm. PD is performed on an outpatient basis with conscious sedation and is most commonly carried out using a guidewire and fluoroscopy to position the balloon but can also be done by placing the balloon across the EGJ under direct endoscopic visualization. An endoscopy is performed beforehand to rule out other pathology, to determine landmarks, and to clear the esophagus of any retained fluid or food. The location of the EGJ can also be marked during the initial endoscopy by making a mental note of its location using fluoroscopy while the tip of the endoscope sits at the EGJ, injecting a small amount of radiopaque contrast material submucosally at this location or using a radiopaque marker placed on the surface of the patient's body corresponding to the tip of the endoscope. Once a guidewire is positioned across the EGJ and into the antrum, the balloon is advanced over the guidewire and positioned so that it straddles the EGJ. Radio-opaque markers inside the balloon facilitate this fluoroscopy-guided positioning. The smallest balloon diameter (30 mm) is usually selected first, with larger diameters used subsequently if response is suboptimal. Proper positioning can be confirmed by inflating a small amount of air into the balloon and observing the position of the LES as it forms a "waist" on the balloon. If necessary, the balloon can then be either advanced or retracted so that the waist is roughly centred on the balloon. The balloon is then rapidly inflated until its waist is seen to flatten out. Reported dilation durations have been variable with many operators holding inflation for a full minute. However, RCTs comparing 15–60 s[34] and 6–60 s[35] have found no difference in the outcome. Reported balloon pressures range from 7–15 psi. In most centres, patients undergoing PD subsequently undergo a gastrograffin swallow (followed by a barium esophagram if no obvious leak seen) to ensure absence of esophageal perforation prior to discharge. This can be done by infusing contrast material endoscopically under fluoroscopic control at the end of the procedure,[36] thereby obviating the need to use the X-ray department and providing an opportunity for prompt endoscopic repair if a perforation is demonstrated. If perforation is strongly suspected on clinical grounds, a contrast study should be avoided. Instead, a computed tomography to assess the presence of free air has been advocated.[37] Most perforations after PD can be treated conservatively, and only a minority require a surgery. Practical details of the PD technique can be reviewed in Video S2.

Predictors of favorable clinical outcomes after PD include female sex, age >45 years, esophageal diameter >3 cm, type II achalasia, increased emptying on post-treatment timed barium esophagram, and LES pressure after dilation of less than 10 mmHg.[38] Recently, the change in EGJ distensibility as measured by the immediate pre- and post-dilation Functional Luminal

Imaging Probe (FLIP) measurements has been reported to accurately predict early clinical success of PD.[39] However, it is unclear whether this provides a practical advantage over early clinical reassessment.

Many centres perform PD on an "as needed" basis, using either the same or an increased balloon diameter depending on the success and duration of symptom relief following the initial procedure. For example, if symptom improvement is suboptimal or the duration of symptom resolution relatively short, then most operators would repeat with a larger balloon. On the other hand, if initial symptom resolution lasts a year or more, repeating with the same diameter balloon makes sense. Alternatively, a protocol involving routine repeat PD with a larger balloon within weeks of the initial procedure (irrespective of initial symptom response) is used by others.[40]

To our knowledge, there are no trials examining the efficacy of PD versus sham dilation. A recent meta-analysis[23] of 52 uncontrolled studies in 4166 achalasia patients found an overall clinical success rate of 83% (95% CI: 79%–85%) with a 3–6 month follow-up. Average resting LES pressure declined from 34 to 21 mmHg. Perforation was reported in 2.8% (95% CI: 2.3%–3.5%), although in one very large series, perforation rate was <0.5%.[41] Bleeding requiring intervention was reported in 2% (95% CI: 1%–4%) and symptomatic gastroesophageal reflux disease (GERD) at 6-month follow-up was 9% (95% CI: 5%–16%). Reported perforation rates are variable depending on clinical context. A contemporary systematic review and meta-analysis which included 10 studies ($n = 643$) revealed that perforations occurred most often during the initial dilation and significantly more often when using a 35-mm balloon (initial and subsequent dilations) than when using a 30-mm balloon (3.2% vs. 1%).[42] When looking only at subsequent dilations using a 35-mm balloon, a repeat dilation was safer than a first dilation (0.97% vs. 9.3%). Ideally, patients selected for PD should be surgical candidates, as surgery may be required in case of perforation.[43]

Over time, the proportion of patients remaining in remission after PD decreases. A retrospective study examining long-term outcomes after single and serial PDs revealed 3-year success rates of 78% and 85%, respectively.[44] Similar results were reported by Richter[45] who performed a retrospective review of 24 studies comprising about 1144 patients. PD with the Rigiflex dilator resulted in good-to-excellent relief of symptoms in 74%, 86% and 90% of patients treated with 30, 35, and 40 mm balloon, respectively. The average time to follow-up was 37 months. A meta-analysis[46] of 21 studies examining PD efficacy and safety in achalasia concluded that most patients needed several PDs over the span of a lifetime to achieve remission. They also found that the use of the Rigiflex dilator and performing several dilations during the initial session were both associated with enhanced efficacy. The 21 studies ($n = 2497$ patients) using a single dilation session exhibited a 1-year efficacy of 66%. This number dropped to 60%, 53%, and 50% at 2, 3, and 5 years, respectively. Only a few of the included studies ($n = 497$ patients) examined the 10-year symptomatic efficacy of PD and revealed that only 25% of patients were still in symptomatic remission after a single dilation session.

A retrospective study published by Zerbib et al.[47] concluded that one-third of 150 achalasia patients treated with PD will have symptomatic relapse within a 4-year period but that long-term remission could be achieved in most patients using on demand PD when achalasia symptoms return. The authors reported an estimated efficacy of 97% and 93% at 5 and 10 years, respectively, but PD had to be repeated frequently. The graded dilation protocol is the best way to achieve long-term results.[40,44,47] As described in the Boeckxstaens trial, each patient undergoes at least two pneumatic dilations.[40] The first is carried out with a 30-mmHg Rigiflex balloon, and the second with a 35-mmHg balloon 1–3 weeks later. Four weeks after the second dilation, a third dilation may be performed with a 40-mmHg balloon if the Eckardt score is still above 3.

Pneumatic dilation is a safe and effective therapeutic alternative after failed laparoscopic Heller myotomy,[45,48] but to date, reported experience with PD in patients who have failed peroral endoscopic myotomy is too limited to draw conclusions.[25]

2.3 | Heller myotomy

Experience with the surgical myotomy has now spanned over a century. Beginning with its first description in 1914 by Ernest Heller,[49] the surgical myotomy has evolved from being an open bilateral procedure to its present state as a single anterior myotomy performed laparoscopically (LHM).[50,51] A recent meta-analysis of 5834 LHM patients from 53 studies (five RCTs and 48 retrospective or prospective cohort studies) found an overall clinical success rate of 88% (95% CI: 87%–89%) over a mean follow-up of 40 months.[52] The most common adverse event noted with LHM is intraprocedural perforation (10%–14%), but perforations can generally be repaired intraoperatively and not lead to clinical sequalae.[40,53–55] The overall rate of mortality associated with LHM is less than 1%, and adverse events requiring post-operative intervention are also rare at 0.6%.[41] Furthermore, conversion to open surgery is also uncommon, occurring in approximately 1% of cases.[56] In the large meta-analysis cited above,[52] post-LHM symptomatic GERD was noted in 17.5%, endoscopic esophagitis in 11.5%, and abnormal reflux as measured by ambulatory pH studies in 11.1%.

Recently, a 5-year follow-up of the European achalasia trial was completed and demonstrated sustained clinical success (Eckardt score ≤ 3) of 84% at 5 years post-LHM.[57] However, it should be noted that efficacy can vary depending on the subtype of achalasia and morphology (advanced sigmoid vs. non-sigmoid). Overall, LHM is less effective for advanced sigmoid and type III achalasia.[58–61]

Outlined in Table 1 are results of selected LHM trials displaying long-term outcome of achalasia patients undergoing LHM.[62–66] Taken together, these represent more than 2000 patients, with follow-up spanning 2.5–17 years. Reported efficacy ranged from 32.2% to 95%. Note that each trial reported efficacy differently from the other trials. The largest ($n = 1001$) trial, by Costantini et al.,[63] is the only one which used the Eckardt score to document efficacy. The authors reported excellent long-term efficacy:

TABLE 1 Outcomes of selected laparoscopic Heller myotomy (LHM) series with 12 ≥ month follow-up

Study	Country	N	Age [range]	Prior treatment (%)	Operating time (min) [range]	Myotomy length (cm) [range]	Follow-up (months)	Efficacy[a] (%)	Reflux[b] (%)	Adverse events, n (%)
Rosemurgy 2010[62]	Tampa, USA	505	49.5 [11–90]	60	[–]	[–]	31	95	[–]	96 (19)
Costantini 2018[63]	Padua, Italy	1001	46 [32–58]	18.2	[–]	[–]	62	89.5	6.5	47 (4.7)
Csendes 2022[64]	Santiago, Chile	89	42.1 [–]	14.6	[–]	[–]	204	78.7	16.9	8 (9)
Krishnamohan 2014[65]	Rochester, USA	500	51 [8–89]	60.6	[–]	[–]	77.5	32.2[c]	[–]	78 (15.6)
Costantino 2020[66]	Boston, USA	130	50 [18–83]	[–]	[–]	7	79	78[d]	[–]	6 (4.9)

Note: [–] Data not available.

[a]As defined by authors. Definitions were different in each study.

[b]Follow-up available on 48.2% of patients. Success was defined by the absence of difficulty swallowing.

[c]As defined by Eckardt Score < 3.

[d]Evidence of gastroesophageal reflux disease (GERD) by 24 pH, endoscopy, and/or GERD questionnaire.

over 80% at 20 years. The patients who failed their LHM subsequently underwent PD, resulting in an overall success rate of 98.4%. Multivariate analysis revealed the following predictors of poor response: chest pain, sigmoid esophagus, and manometric pattern. Abnormal esophageal acid exposure was documented in 9.1% of patients during post-operative 24 h pH studies. The study by Krishnamohan et al.[65] reported 32.2% efficacy. In this trial, follow-up data were only available for less than half of the patients, and efficacy was defined as the absence of any difficulty swallowing. Rosemurgy et al.[62] reported a 95% efficacy which they defined as patients having symptoms less than once per week.

Despite over two decades of experience with LHM, there remains controversy over whether an antireflux procedure (ARP) is required. This is due to the fact that some groups report a low incidence of reflux post-LHM without ARP.[67] In a meta-analysis by Campos et al.[55] that included over 3000 patients receiving LHM, there was a significantly lower incidence of reflux in patients that received an ARP 8.8% (0%–44%) than those who did not (31.5%). A debate ensued on whether ARP patients should receive partial anterior fundoplication (Dor) or posterior fundoplication (Toupet). In a prospective RCT of 60 patients, Rawlings et al.[68] compared the Dor with the Toupet and did not find a statistically significant difference in abnormal acid exposure between the two groups based on 24 h pH (Dor 41.7% vs. Toupet 21%, $p = 0.152$). Therefore, current guidelines recommend ARP but do not specify a preference between Dor or Toupet. The Dor fundoplication is more often used by operators as it is typically a faster and simpler procedure, results in less disruption of the hiatal anatomy, and offers coverage of the esophageal mucosa with the fundus, which proves to be useful if a perforation has occurred. A video demonstrating key features of the LHM procedure can be found at the following external link.

A challenging scenario arises in patients who have undergone a LHM that either fails to control their symptoms adequately or symptoms recur after initial success. The most common cause of treatment failure or recurrent symptoms after LHM is an incomplete myotomy,[69] and more specifically, with failure to extend the myotomy at least 2–3 cm distal to the GE junction.[56,70–72] Other less common causes include a tight or disrupted fundoplication, severe reflux, or severe fibrosis. The general approach in repeat LHM is to take down adhesions from the prior surgery, liberate the esophagus, take down the prior fundoplication, confirm the depth and length of prior myotomy, and subsequently complete the myotomy, as necessary.[73] Reoperation is more complicated and should be undertaken at an expert centre as these procedures have a higher incidence of complications, longer operative time, and lower success rate than those without prior surgical myotomy.[74]

2.4 | Peroral endoscopy myotomy

Peroral endoscopy myotomy (POEM) is performed worldwide with thousands of cases successfully completed. The various adverse events described in the literature include mucosal injury, esophageal

perforation, serious bleeding, pneumothorax, pneumomediastinum, pneumoperitoneum, pneumopericardium, infection, aspiration, and gastroesophageal reflux. Apart from reflux, these adverse events are generally quite rare. In the largest single-centre series that emerged from Shanghai, China, the major adverse event rate was 3.3% in 1680 patients.[75] However, the majority of these were due to the use of air insufflation. After the introduction of carbon dioxide insufflation and increased experience, the major adverse event rate dropped to about 1% at the same centre. This is consistent with the most recent multicenter study with 1826 patients that demonstrated a severe adverse event rate of 0.5%.[76] In the most recent systematic review which included 36 studies and 2373 patients, the overall rate of reported adverse events varied from 0.2% for major bleeding and up to 7.5% for subcutaneous emphysema.[77] Not surprisingly, the adverse event rate reported in different series varies from 0%–41%.[78,79] This variability is multifactorial and likely a result of differences in operator experience, technique, and equipment used, as well as classification and reporting of adverse events.[80] An example regarding equipment variation resulting in differences in adverse events is demonstrated in a series of 220 POEMs, where the first 42 cases used low-flow CO_2 that resulted in an incidence of tense pneumoperitoneum of 28%. In the subsequent 120 cases "ultra-low" flow CO_2 was used, which resulted in a 10% incidence of tense pneumoperitoneum.[81]

As experience with POEM increases, the initial reported success appears to be durable. Excellent results have been demonstrated with 12-, 24-, and 36-month follow-up with sustained clinical success (Eckardt ≤ 3) of 98%, 91%, and 89%, respectively.[82,83] There is now also emerging data of 5-year follow-up with success rates of over 80%.[84] Table 2 demonstrates excellent clinical results in multiple series worldwide that reported on at least 100 patients and 12 month follow-up.[81,85–93] Nearly all published series with long-term follow-up have demonstrated excellent efficacy. However, there is the multicentered European study that demonstrated only 78% efficacy with over 2-year follow-up.[94] It is hypothesized that since many of patients that had relapsed were the first cases performed by the various operators, and the myotomies were likely incomplete. This is due to the fact that it is well-known from the LHM literature that if a myotomy is not extended 2–3 cm onto the gastric side, it results in persistent or early recurrence of symptoms (see previous section). This series reinforces the importance of adequate training of POEM operators prior to their independent practice.

Peroral endoscopy myotomy can be successfully applied to patients who have had prior surgical myotomy or previous POEM. In patients with prior surgical myotomy with wrap, the anatomy at the EGJ may be distorted and exhibit increased fibrosis. Despite being able to avoid the area most heavily affected by fibrosis (anterior), the posterior position still may have dense fibrosis. However, if performed by experienced operators, success rates remain over 90% with low complication rates, similar to treatment-naive patients.[95–98] In a recent multicentre study that included 90 patients from 13 centres worldwide, the post-LHM patients had a clinical success rate of 81% with a median follow-up of 8.5 months.[95]

The two most common sites of POEM are the posterior (5 o'clock) and the anterior (1–2 o'clock) positions. There are numerous theoretical advantages/disadvantages to these two main approaches that have been discussed elsewhere.[99] Currently, there is no consensus regarding the optimum position of the myotomy site, and it is primarily based on operator preference. (To view video demonstrating details of the POEM technique, see Video S3). To date, there are five RCTs that have examined this topic with a total of 626 patients.[100–104] A meta-analysis of four of these trials[105] found that there was no significant difference between the two approaches with respect to short-term clinical efficacy, procedure time, manometric outcomes, and incidence of GERD. However, the posterior approach was associated with fewer adverse events and shorter time to close the mucosal incision.[105] Similarly, a more recent systematic review and meta-analysis that included both randomized studies (488 patients) and non-randomized studies (759 patients) found no significant difference between approaches with respect to clinical efficacy, adverse events, and incidence of GERD.[106] However, the posterior approach did have an overall shorter mean procedure time (62.1 min, 95% CI 48.5–75.7) than the anterior approach (82.7 min, 95% CI 69.0–96.4).

There is ongoing debate regarding whether the optimal myotomy technique should be a selective circular versus full thickness (circular and longitudinal muscle) myotomy. The theoretical arguments for full thickness myotomy include a reduced procedure time and improved efficacy of the myotomy. However, arguments against this are increased risk of complications, post-procedural GERD, and development of esophageal diverticulum. In a retrospective series of 234 patients, there was a reduction in procedure time with a full thickness myotomy as compared to selective circular myotomy (41.7 ± 18.9 vs. 48.9 ± 28.6 min) without any difference in macroscopic esophagitis on follow-up (21.2% vs. 16.5%, $p = 0.38$).[79] Similar results were found in two other retrospective series that demonstrated reduced procedure time and no difference in reflux rate.[86,107] Another retrospective series of 56 patients also did not find a difference between selective versus full thickness myotomy with respect to GERD symptoms (15.6% vs. 33.3%, $p = 0.12$), abnormal acid exposure on 24 h pH (40.6% vs. 50%, $p = 0.485$), or esophagitis (15.6% vs. 29.2%, $p = 0.222$).[108] However, when the authors examined clinically relevant GERD, defined as abnormal esophageal acid exposure associated with GERD symptoms and/or esophagitis, there was a significant difference between selective versus full thickness myotomy (12.5% vs. 37.5%, $p = 0.028$). In brief, based on the available literature, there is reduced procedure time with a full thickness myotomy; however, there is insufficient evidence to make a definitive statement regarding reflux incidence and/or complications.

There is ongoing debate regarding post-POEM gastroesophageal reflux (GER) and GERD. The reported incidences of post-POEM GERD vary considerably from 0%–58%.[109,110] One of the most significant reasons for this is wide variability in the definitions and testing used to diagnose post-POEM GERD.

In 2018, Repici et al.[111] published a systematic review and meta-analysis that included 17 POEM studies. Post-POEM it was

TABLE 2 Outcomes of selected POEM series with ≥100 patients with 12 ≥ months follow-up

Study	Country	*N*	Age [range]	Prior treatment (%)	Operating time (min) [range]	Myotomy length (cm) [range]	Follow-up (months)	Efficacy[a] (%)	Reflux[b] (%)	Minor/major adverse events[c] *n*/*n* (%/%)
Sharata 2014[85]	Portland, USA	100	58 [18–83]	35	128 [45–215]	8 [4–23]	16	98	38.2	17/1 (17/1)
Ramchandani 2015[81]	Hyderabad, India	220	39 [9–74]	41.4	88 [38–180]	12 [6–19]	13.4	92	16	77/0 (35.0/0)
Duan 2015[86]	Changsha, China	123	42.1 [–]	14.6	59.6 [–]	10.5 [–]	21	98.4	1.6	14/0 (11.3/0)
Inoue 2015[87]	Tokyo, Japan	500	43 [32–58]	40.6	90 [70.8–119]	14 (12–16)	12–24[d]	91	19.4	16/0 (3.2/0)
Hungness 2016[88]	Chicago, USA	115	52.9 [–]	30	101 [–]	10.7 [–]	28.8	92	40	17/3 (15.2/2.7)
Nabi 2017[89]	Hyderbad, India	408	40 [4–77]	45	76.6 [30–180]	13 [6–21]	17	91	28.3	141/0 (34.6/0)
Ngamruengphong 2017[82]	Multicenter	205	49 [–]	39.5	[–]	11.9 [–]	31	91	37.5	16/1 (7.8/0.5)
Li 2018[90]	Shanghai, China	564	38 [6–77]	34.2	45 [15–202]	10 [5–17]	49	88.6	37.3	126/9 (22.3/1.6)
Werner 2019[91]	Multicenter	112	78.6 [–]	34.8	[–]	[–]	24	83	28	12/3 (11/3)
Shiwaku 2020[92]	Multicenter	1346	47.2 [3–95]	31	99.6 [–]	13.6 [–]	12	94.7	63	50/0 (3.7/0)
McKay 2021[93]	Portland, USA	100	57 [20–88]	29	[–]	9 [2–23]	75	79	[–]	[–]

Note: [–] Data not available.

[a]Eckardt ≤3.

[b]Evidence of gastroesophageal reflux disease (GERD) by 24 pH, endoscopy, and/or GERD questionnaire.

[c]1–2-year follow-up available on 74% of patients.

[d]Minor = Clavian Dindo Grade I-IIIa, Major = Clavian Dindo Grade IIIb-V.

revealed abnormal 24-h pH testing and esophagitis occurred in 39% (95% CI, 24.5%–55.8%) and 29.4% (95% CI, 18.5%–43.3%) of patients, respectively. In patients that developed esophagitis, 4.47% (95% CI, 3.27%–6.07%) were Los Angeles (LA) grade C or D. Repici et al. acknowledged limitations in the literature that included study heterogeneity and publication bias. More recently in the prospective randomized trial comparing POEM to LHM with Dor's fundoplication by Werner et al.,[91] the incidence of reflux esophagitis at 24 months was 44% after POEM as compared with 29% after LHM. Based on these results, authors initially concluded that reflux was more common in patients undergoing POEM versus LHM. However, after this flawed conclusion was pointed out, they completed a post-hoc analysis using the Lyon consensus definition of GERD. Using this standardized definition, it was found that at 2-years follow-up, there was no significant difference between POEM and LHM, 28% vs. 29%, respectively. This highlights the challenge in interpretation of the reported incidences of post-POEM GERD and why they vary widely. To best estimate the true incidence of post-treatment GERD in achalasia patients the application of the Lyon Consensus will allow for a more balanced comparison between studies and treatment modalities.[112] An in-depth discussion of post-POEM GERD is beyond the scope if this review and a detailed examination of this can be found elsewhere.[113]

There is mounting evidence that using FLIP intraoperatively can be useful in guiding the myotomy both during LHM[114] and POEM[115] to ensure that the distensibility of the EGJ has been normalized. In a recent retrospective analysis, Holmstrom et al.[116] reported that intraoperative use of FLIP during POEM leads to modification of the myotomy (i.e. by extension of the myotomy proximally or distally, including the longitudinal muscle in the myotomy, or incising additional circular muscle fibers that had been overlooked), in 65% of patients. Outcomes also were reported improved in patients in which FLIP was used.

2.5 | Other therapies

Injection of sclerosing agents (ethanolamine and polidocanol) into the LES of achalasia patients may provide symptom improvement comparable to BoTox,[117,118] presumably by damaging excitatory neurons and thereby lowering resting LES pressure. However, repeated injections appear to be required, raising concerns about long-term fibrosis and stricture formation.

Although studies are limited, temporary (1 month) placement of removable, self-expanding metal stents across the EGJ appears efficacious in achalasia patients.[119,120] Using 30-mm diameter stents is optimal, with one study reporting a 10-year symptom remission rate of >85%.[119] Based on current evidence, however, neither stenting or sclerotherapy can be recommended as treatment for achalasia, particularly given the other well-established treatments that are currently available.[25]

Rarely, esophagectomy needs to be considered in patients with end-stage achalasia who have failed less invasive surgical or endoscopic treatment methods.[25] A contemporary systematic review reported a pooled prevalence of pneumonia, anastomotic leakage, and mortality of 10%, 7%, and 2%, respectively.[121]

2.6 | Comparative controlled clinical trials

The last decade has seen several RCTs published that directly compare efficacy of different treatment modalities for achalasia. A number of outcome measures have been used, but in the majority of studies, a successful clinical outcome is defined as an Eckardt symptom score of ≤3. In interpreting these studies, one needs to consider differences in the technical application of the therapy (such as number of repeat PDs allowed before establishing clinical failure) as well as the time frame of the defined outcome.

2.6.1 | BoTox versus lapascopic Heller myotomy

Zaninotto et al.[122] compared outcomes of 40 patients randomized to BoTox injections (two injections 1 month apart providing initial injection resulted in >50% symptom improvement) to 40 patients randomized to LHM with fundoplication. At 6-month follow-up, symptom improvement was somewhat greater in the LHM group (82% vs. 66%). However, the chance of being symptom-free at 2 years was only 34% in the BoTox group versus 87.5% in those undergoing LHM. Interestingly, at 6 months post-treatment resting LES pressure and LES nadir pressures were not significantly different, although esophageal diameter as measured by barium swallow had only decreased significantly in the LHM group.

2.6.2 | Pneumatic dilation versus BoTox

A recent metanalysis of several small RCTs comparing PD to BoTox[24] found similar outcomes between the two treatment modalities at 4 weeks, but more favorable results were noted with PD at 6 months (80.7% vs. 51.8%) and 1 year (73.3% vs. 37.5%).

2.6.3 | Pneumatic dilation versus laparoscopic Heller myotomy

A total of five RCTs involving 498 patients have been reported comparing PD to LHM. A meta-analysis of these trials found that the overall success rate was higher for LHM at 3 months (RR 1.16, $p = 0.04$) and 1 year (RR 1.14, $p = 0.02$); however, there was no difference at the 2- and 5-year follow-up.[123] Table 3 highlights results from RCTs comparing LHM to PD for management of achalasia.[40,57,124–127] While the multicenter trials by Boeckxstaens et al.[40] and Moonen et al.[57] displayed comparable efficacy results between the two treatment modalities, the other single-center trials tended to favor LHM. It is important to note that there was considerable disparity

TABLE 3 Randomized controlled trials (RCTs) comparing laparoscopic heller myotomy (LHM) to pneumatic dilation (PD) for the management of achalasia

Author	Study design	Inclusion criteria	Study population	Outcome
Kostic et al. 2007[124]	Single centre randomized trial comparing LHM vs. PD	Newly diagnosed achalasia patients	51 patients	Cumulative number of treatment failures at 12 months: six treatment failures in the PD group 1 treatment failure in the LHM group ($p = 0.04$).
Borges et al. 2014[125]	Single centre randomized trial comparing LHM vs. PD	Newly diagnosed achalasia patients	92 patients	After 12 and 24 months, 57/86 (66.3%) and 42/74 (56.8%) patients reported good results.
Persson et al. 2015[126]	Single centre randomized trial LHM vs. repeated PD	Newly diagnosed achalasia patients	53 patients	At 5 years follow-up, 10 patients (36%) in the dilatation group and two patients (8%) in the myotomy group were classified as failures ($p = 0.016$).
Hamdy et al. 2015[127]	Prospective randomized controlled trial comparing LHM vs. PD	Adult patients (20–50 years old) who presented with early stage achalasia (esophageal diameter of <3.5 cm on contrast esophagography)	50 patients	The rate of symptoms relief was 76% in EPD compared with 96% in LEM ($p = 0.04$).
Boeckxstaens et al. 2011[40] and Moonen et al. 2016[57]	Multicentre randomized trial comparing LHM vs. PD	Newly diagnosed achalasia patients	201 patients	At 5 years follow-up, success rates for LHM (84%) and PD (82%) are comparable.

between studies in how efficacy was reported, as well as the duration of follow-ups.

2.6.4 | Pneumatic dilation versus peroral endoscopic myotomy

To date, there has been one RCT, involving 133 adult patients, comparing PD to POEM.[128] Clinical success at 2 years was achieved in 92% in the POEM group versus 54% in the PD group ($p < 0.001$). However, it is noteworthy that the balloon inflation pressures used in this study were quite low (8 PSI), and the success rate for PD rose to 76% if patients who subsequently underwent dilation with a 40-mm balloon were included. Post-treatment reflux esophagitis developed in 41% of the POEM group versus 7% in the PD group ($p = 0.002$). The authors did not report specific numbers of achalasia subtypes allocated to the two treatment arms, but in an appendix, reported no statistically significant difference in response rates based on achalasia subtype.

2.7 | Peroral endoscopic myotomy versus laparoscopic Heller myotomy

The first randomized controlled trial comparing POEM to LHM was recently published.[91] This study randomized 112 patients to POEM and 109 to LHM with Dor's fundoplication. Clinical success rates at 2 years were similar (83% for POEM; 81.7% for LHM). Serious adverse events were numerically higher in the LHM group (7.3% vs. 2.7%), but this was not statistically significant. The incidence of post-operative reflux esophagitis was higher in the POEM group (57% vs. 20% at 2 months; 44% vs. 29% at 2 years). The majority of patients enrolled had type II achalasia. Outcomes in patients with type III achalasia were similar in the two treatment arms, with 10 of 12 (83%) achieving clinical success with POEM and 7 of 9 (79%) with LHM.

A recent case–control study using propensity scoring match with 140 patients in each treatment group reported similar midterm outcomes for POEM and LHM.[129] Four years after treatment, clinical success rates were >90% and not significantly different between the two treatments. Esophagitis was documented in 37.4% of patients who underwent POEM and in 15.2% of patients who underwent LHM.

3 | CONCLUSIONS AND RECOMMENDATIONS

The last 10–15 years has seen a resurgence of interest in the evaluation of therapies for achalasia. Unfortunately, there has been little progress in the development of effective pharmacological treatments. Oral or sublingual smooth muscle relaxants may have some efficacy in select patients, but they are rarely useful for long-term

control of symptoms. BoTox injection provides some relief of symptoms in the majority of patients but requires periodic reinjection that may provide progressively less benefit over time. It may be more efficacious in elderly patients and those with type III achalasia.[28] It is therefore currently recommended that BoTox be reserved for achalasia patients who are poor candidates for more invasive interventions.[25]

We now have three well-established, safe and effective therapies, PD, LHM, and POEM that, if applied properly, can lead to marked symptom improvement in the vast majority of patients. However, future retreatment may be required for all treatments, but in particular PD. Which treatment is offered first often depends on local expertise.

A recent guideline published by the Society of American Gastrointestinal and Endoscopic Surgeons[130] recommended POEM over PD as initial treatment of achalasia (without specifying different achalasia subtypes), based on their meta-analysis of comparative trials.[131] They also suggested using either POEM or LHM in type I and II achalasia initially and POEM for type III achalasia, based on "very low certainty" evidence. However, as pointed out by de Heer et al.,[132] meta-analysis of trials involving PD are unreliable because of the widely variable PD technique and outcome measures. Furthermore, type II achalasia, the most common subtype, is also the most responsive to therapy, and in the large European controlled clinical trial comparing PD to LHM,[40] PD was slightly more effective than LHM in patients with this subtype. Because of this, the lower incidence of reflux and cost-effective analysis that favor PD over LHM as initial therapy for achalasia,[133,134] a case can be made for offering PD as first line therapy in type II achalasia, with either POEM or LHM used when response to PD is inadequate. Recent studies suggest that POEM is more cost-effective than LHM,[135–137] but currently this evidence alone is not strong enough to justify choosing POEM over LHM in the treatment of achalasia. Although the recent RCT comparing LHM to POEM[91] did not find differences in outcome in Type III achalasia, the numbers were small, and there is evidence from larger case-controlled series[59,138] that POEM is the preferred option for type III achalasia because it allows tailored proximal extension of the myotomy to deal with the spastic contractions of the esophageal body. Despite this apparent advantage in favor of POEM, it may result in an increased frequency of reflux esophagitis. However, in the post-hoc analysis of the randomized control trial of POEM versus LHM,[91] the incidence of GERD using the Lyon consensus failed to demonstrate any clinically significant difference at 2 years after POEM or LHM.[139]

As this review demonstrates, advances in both the art and science of achalasia therapy have been impressive in recent years, and it is hoped that future studies will lead to better tailoring of therapy to the pathophysiology in individual patients.

AUTHOR CONTRIBUTIONS

All three authors contributed to the writing and editing of this manuscipt.

FUNDING INFORMATION

No funding declared.

CONFLICT OF INTEREST

No competing interests declared.

ORCID

Robert Bechara https://orcid.org/0000-0002-4543-5580

REFERENCES

1. Stein CM, Gelfand M, Taylor HG. Achalasia in Zimbabwean blacks. *S Afr Med J*. 1985;67:261-262.
2. Sadowski DC, Ackah F, Jiang B, Svenson LW. Achalasia: incidence, prevalence and survival. A population-based study. *Neurogastroenterol Motil*. 2010;22:e256-e261. doi:10.1111/j.1365-2982.2010.01511.x
3. Samo S, Carlson DA, Gregory DL, Gawel SH, Pandolfino JE, Kahrilas PJ. Incidence and prevalence of achalasia in Central Chicago, 2004–2014, since the widespread use of high-resolution manometry. *Clin Gastroenterol Hepatol*. 2017;15:366-373. doi:10.1016/j.cgh.2016.08.030
4. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology*. 2008;135:1526-1533. doi:10.1053/j.gastro.2008.07.022
5. Paterson WG. Etiology and pathogenesis of achalasia. *Gastrointest Endosc Clin N Am*. 2001;11:249-266.
6. Tlottrup A, Forman A, Funch-Jensen P, Raundahl U, Andersson KE. Effects of postganglionic nerve stimulation in oesophageal achalasia: an in vitro study. *Gut*. 1990;31:17-20.
7. Holloway RH, Dodds WJ, Helm JF, Hogan WJ, Dent J, Arndorfer RC. Integrity of cholinergic innervation to the lower esophageal sphincter in achalasia. *Gastroenterology*. 1986;90:924-929. doi:10.1016/0016-5085(86)90869-3
8. Paterson WG. Esophageal and lower esophageal sphincter response to balloon distention in patients with achalasia. *Dig Dis Sci*. 1997;42:106-112. doi:10.1023/a:1018893206926
9. Lendrum FC. Anatomic features of the cardiac orifice of the stomach: with special reference to cardiospasm. *Arch Intern Med*. 1937;59:474-511. doi:10.1001/archinte.1937.00170190109007
10. Misiewicz JJ, Waller SL, Anthony PP, Gummer JW. Achalasia of the cardia: pharmacology and histopathology of isolated cardiac sphincteric muscle from patients with and without achalasia. *Q J Med*. 1969;38:17-30.
11. Raymond L, Lach B, Shamji FM. Inflammatory aetiology of primary oesophageal achalasia: an immunohistochemical and ultrastructural study of Auerbach's plexus. *Histopathology*. 1999;35:445-453. doi:10.1046/j.1365-2559.1999.035005445.x
12. Csendes A, Smok G, Braghetto I, et al. Histological studies of Auerbach's plexuses of the oesophagus, stomach, jejunum, and colon in patients with achalasia of the oesophagus: correlation with gastric acid secretion, presence of parietal cells and gastric emptying of solids. *Gut*. 1992;33:150-154. doi:10.1136/gut.33.2.150
13. Goldblum JR, Whyte RI, Orringer MB, Appelman HD. Achalasia. A morphologic study of 42 resected specimens. *Am J Surg Pathol*. 1994;18:327-337.
14. Goldblum JR, Rice TW, Richter JE. Histopathologic features in esophagomyotomy specimens from patients with achalasia. *Gastroenterology*. 1996;111:648-654. doi:10.1053/gast.1996.v111.pm8780569

15. Sodikoff JB, Lo AA, Shetuni BB, Kahrilas PJ, Yang GY, Pandolfino JE. Histopathologic patterns among achalasia subtypes. *Neurogastroenterol Motil*. 2016;28:139-145. doi:10.1111/nmo.12711
16. Bassotti G, Annese V. Review article: pharmacological options in achalasia. *Aliment Pharmacol Ther*. 1999;13:1391-1396. doi:10.1046/j.1365-2036.1999.00645.x
17. Traube M, Dubovik S, Lange RC, McCallum RW. The role of nifedipine therapy in achalasia: results of a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol*. 1989;84:1259-1262.
18. Triadafilopoulos G, Aaronson M, Sackel S, Burakoff R. Medical treatment of esophageal achalasia. Double-blind crossover study with oral nifedipine, verapamil, and placebo. *Dig Dis Sci*. 1991;36:260-267. doi:10.1007/BF01318193
19. Bortolotti M, Coccia G, Brunelli F, et al. Isosorbide dinitrate or nifedipine: which is preferable in the medical therapy of achalasia? *Ital J Gastroenterol*. 1994;26:379-382.
20. Ferreira-Filho LP, Patto RJ, Troncon LE, Oliveira RB. Use of isosorbide dinitrate for the symptomatic treatment of patients with Chagas' disease achalasia. A double-blind, crossover trial. *Braz J Med Biol Res*. 1991;24:1093-1098.
21. Pasricha PJ, Ravich WJ, Kalloo AN. Effects of intrasphincteric botulinum toxin on the lower esophageal sphincter in piglets. *Gastroenterology*. 1993;105:1045-1049. doi:10.1016/0016-5085(93)90947-b
22. Pasricha PJ, Ravich WJ, Hendrix TR, Sostre S, Jones B, Kalloo AN. Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med*. 1995;332:774-778. doi:10.1056/NEJM199503233321203
23. Khashab MA, Vela MF, Thosani N, et al. ASGE guideline on the management of achalasia. *Gastrointest Endosc*. 2020;91:213-227.e6. doi:10.1016/j.gie.2019.04.231
24. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev*. 2014;CD005046. doi:10.1002/14651858.CD005046.pub3
25. Zaninotto G, Bennett C, Boeckxstaens G, et al. The 2018 ISDE achalasia guidelines. *Dis Esophagus*. 2018;31:doy071. doi:10.1093/dote/doy071
26. Vaezi MF, Richter JE, Wilcox CM, et al. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut*. 1999;44:231-239. doi:10.1136/gut.44.2.231
27. Annese V, Basciani M, Perri F, et al. Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. *Gastroenterology*. 1996;111:1418-1424. doi:10.1016/s0016-5085(96)70002-1
28. Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. *Gastroenterology*. 1996;110:1410-1415. doi:10.1053/gast.1996.v110.pm8613045
29. Annese V, Bassotti G, Coccia G, et al. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. GISMAD Achalasia Study Group. *Gut*. 2000;46:597-600. doi:10.1136/gut.46.5.597
30. Horgan S, Hudda K, Eubanks T, McAllister J, Pellegrini CA. Does botulinum toxin injection make esophagomyotomy a more difficult operation? *Surg Endosc*. 1999;13:576-579. doi:10.1007/s004649901044
31. Hoffman BJ, Knapple WL, Bhutani MS, Verne GN, Hawes RH. Treatment of achalasia by injection of botulinum toxin under endoscopic ultrasound guidance. *Gastrointest Endosc*. 1997;45:77-79. doi:10.1016/s0016-5107(97)70306-7
32. Martinek J, Siroký M, Plottová Z, Bures J, Hep A, Spicák J. Treatment of patients with achalasia with botulinum toxin: a multicenter prospective cohort study. *Dis Esophagus*. 2003;16:204-209. doi:10.1046/j.1442-2050.2003.00329.x
33. van Hoeij FB, Tack JF, Pandolfino JE, et al. Complications of botulinum toxin injections for treatment of esophageal motility disordersdagger. *Dis Esophagus*. 2017;30:1-5. doi:10.1111/dote.12491
34. Gideon RM, Castell DO, Yarze J. Prospective randomized comparison of pneumatic dilatation technique in patients with idiopathic achalasia. *Dig Dis Sci*. 1999;44:1853-1857. doi:10.1023/a:1018898824135
35. Khan AA, Shah SWH, Alam A, Butt AK, Shafqat F, Castell DO. Pneumatic balloon dilation in achalasia: a prospective comparison of balloon distention time. *Am J Gastroenterol*. 1998;93:1064-1067. doi:10.1111/j.1572-0241.1998.00330.x
36. Bechara R, Kortan PP, Schwartz IB, May GR, Kandel G, Marcon NE. Tu1366 immediate combined endoscopic and radiographic evaluation of the esophagus after balloon dilation for achalasia is sufficient to detect leaks in asymptomatic patients. *Gastrointest Endosc*. 2014;79:AB514. doi:10.1016/j.gie.2014.02.812
37. Torresan F, Ioannou A, Azzaroli F, Bazzoli F. Treatment of achalasia in the era of high-resolution manometry. *Ann Gastroenterol*. 2015;28:301-308.
38. Patel DA, Kim HP, Zifodya JS, Vaezi MF. Idiopathic (primary) achalasia: a review. *Orphanet J Rare Dis*. 2015;10:89. doi:10.1186/s13023-015-0302-1
39. Wu PI, Szczesniak MM, Craig PI, et al. Novel intra-procedural distensibility measurement accurately predicts immediate outcome of pneumatic dilatation for idiopathic achalasia. *Am J Gastroenterol*. 2018;113:205-212. doi:10.1038/ajg.2017.411
40. Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med*. 2011;364:1807-1816. doi:10.1056/NEJMoa1010502
41. Lynch KL, Pandolfino JE, Howden CW, Kahrilas PJ. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. *Am J Gastroenterol*. 2012;107:1817-1825. doi:10.1038/ajg.2012.332
42. van Hoeij FB, Prins LI, Smout A, Bredenoord AJ. Efficacy and safety of pneumatic dilation in achalasia: a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2019;31:e13548. doi:10.1111/nmo.13548
43. Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol*. 2013;108:1238-1249; quiz 1250. doi:10.1038/ajg.2013.196
44. Hulselmans M, Vanuytsel T, Degreef T, et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Clin Gastroenterol Hepatol*. 2010;8:30-35. doi:10.1016/j.cgh.2009.09.020
45. Richter JE. Update on the management of achalasia: balloons, surgery and drugs. *Expert Rev Gastroenterol Hepatol*. 2008;2:435-445. doi:10.1586/17474124.2.3.435
46. Katzka DA, Castell DO. Review article: an analysis of the efficacy, perforation rates and methods used in pneumatic dilation for achalasia. *Aliment Pharmacol Ther*. 2011;34:832-839. doi:10.1111/j.1365-2036.2011.04816.x
47. Zerbib F, Thétiot V, Richy F, Benajah DA, Message L, Lamouliatte H. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol*. 2006;101:692-697. doi:10.1111/j.1572-0241.2006.00385.x
48. Familiari P, Greco S, Volkanovska A, et al. Achalasia: current treatment options. *Expert Rev Gastroenterol Hepatol*. 2015;9:1101-1114. doi:10.1586/17474124.2015.1052407
49. Heller E. Extramukose kardioplastik beim chronischen kardiospasmus mit dilatation des oesophagus. *Mitt Grenzgeb Med Chir*. 1914;27:141-149.
50. Pellegrini C, Wetter LA, Patti M, et al. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. *Ann Surg*. 1992;216:291-296; discussion 296-299.

51. Shimi S, Nathanson LK, Cuschieri A. Laparoscopic cardiomyotomy for achalasia. *J R Coll Surg Edinb*. 1991;36:152-154.
52. Schlottmann F, Luckett DJ, Fine J, Shaheen NJ, Patti MG. Laparoscopic Heller myotomy versus peroral endoscopic myotomy (POEM) for achalasia: a systematic review and meta-analysis. *Ann Surg*. 2018;267:451-460. doi:10.1097/SLA.0000000000002311
53. Youssef Y, Richards WO, Sharp K, et al. Relief of dysphagia after laparoscopic Heller myotomy improves long-term quality of life. *J Gastrointest Surg*. 2007;11:309-313. doi:10.1007/s11605-006-0050-6
54. Donahue PE, Horgan S, Liu KJ, Madura JA. Floppy dor fundoplication after esophagocardiomyotomy for achalasia. *Surgery*. 2002;132:716-722; discussion 722-713.
55. Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg*. 2009;249:45-57. doi:10.1097/SLA.0b013e31818e43ab
56. Zaninotto G, Costantini M, Rizzetto C, et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single Centre experience. *Ann Surg*. 2008;248:986-993. doi:10.1097/SLA.0b013e3181907bdd
57. Moonen A, Annese V, Belmans A, et al. Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. *Gut*. 2016;65:732-739. doi:10.1136/gutjnl-2015-310602
58. Rohof WO, Salvador R, Annese V, et al. Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology*. 2013;144:718-725; quiz e713-e714. doi:10.1053/j.gastro.2012.12.027
59. Kumbhari V, Tieu A, Onimaru M, et al. Peroral endoscopic myotomy (POEM) vs laparoscopic Heller myotomy (LHM) for the treatment of type III achalasia in 75 patients: a multicenter comparative study. *Endosc Int Open*. 2015;3:E195-E201. doi:10.1055/s-0034-1391668
60. Schuchert MJ, Luketich JD, Landreneau RJ, et al. Minimally invasive surgical treatment of sigmoidal esophagus in achalasia. *J Gastrointest Surg*. 2009;13:1029-1035; discussion 1035-1026. doi:10.1007/s11605-009-0843-5
61. Salvador R, Costantini M, Zaninotto G, et al. The preoperative manometric pattern predicts the outcome of surgical treatment for esophageal achalasia. *J Gastrointest Surg*. 2010;14:1635-1645. doi:10.1007/s11605-010-1318-4
62. Rosemurgy AS, Morton CA, Rosas M, Albrink M, Ross SB. A single institution's experience with more than 500 laparoscopic Heller myotomies for achalasia. *J Am Coll Surg*. 2010;210:637-645, 645-647. doi:10.1016/j.jamcollsurg.2010.01.035
63. Costantini M, Salvador R, Capovilla G, et al. A thousand and one laparoscopic Heller myotomies for esophageal achalasia: a 25-year experience at a single tertiary center. *J Gastrointest Surg*. 2019;23:23-35. doi:10.1007/s11605-018-3956-x
64. Csendes A, Orellana O, Figueroa M, Lanzarini E, Panza B. Long-term (17 years) subjective and objective evaluation of the durability of laparoscopic Heller esophagomyotomy in patients with achalasia of the esophagus (90% of follow-up): a real challenge to POEM. *Surg Endosc*. 2022;36:282-291. doi:10.1007/s00464-020-08273-1
65. Krishnamohan P, Allen MS, Shen KR, et al. Long-term outcome after laparoscopic myotomy for achalasia. *J Thorac Cardiovasc Surg*. 2014;147:730-736; discussion 736-737. doi:10.1016/j.jtcvs.2013.09.063
66. Costantino CL, Geller AD, Visenio MR, Morse CR, Rattner DW. Outcomes of laparoscopic Heller myotomy for achalasia: 22-year experience. *J Gastrointest Surg*. 2020;24:1411-1416. doi:10.1007/s11605-020-04586-7
67. Robert M, Poncet G, Mion F, Boulez J. Results of laparoscopic Heller myotomy without anti-reflux procedure in achalasia. Monocentric prospective study of 106 cases. *Surg Endosc*. 2008;22:866-874. doi:10.1007/s00464-007-9600-6
68. Rawlings A, Soper NJ, Oelschlager B, et al. Laparoscopic dor versus Toupet fundoplication following Heller myotomy for achalasia: results of a multicenter, prospective, randomized-controlled trial. *Surg Endosc*. 2012;26:18-26. doi:10.1007/s00464-011-1822-y
69. Gouda BP, Nelson T, Bhoyrul S. Revisional surgery after heller myotomy for treatment of achalasia: a comparative analysis focusing on operative approach. *Indian J Surg*. 2012;74:309-313. doi:10.1007/s12262-011-0402-7
70. Di Martino N, Monaco L, Izzo G, et al. The effect of esophageal myotomy and myectomy on the lower esophageal sphincter pressure profile: intraoperative computerized manometry study. *Dis Esophagus*. 2005;18:160-165. doi:10.1111/j.1442-2050.2005.00471.x
71. Wright AS, Williams CW, Pellegrini CA, Oelschlager BK. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. *Surg Endosc*. 2007;21:713-718. doi:10.1007/s00464-006-9165-9
72. Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. *Arch Surg*. 2003;138:490-495; discussion 495-497. doi:10.1001/archsurg.138.5.490
73. Gorecki PJ, Hinder RA, Libbey JS, Bammer T, Floch N. Redo laparoscopic surgery for achalasia. *Surg Endosc*. 2002;16:772-776. doi:10.1007/s00464-001-8178-7
74. Veenstra BR, Goldberg RF, Bowers SP, Thomas M, Hinder RA, Smith CD. Revisional surgery after failed esophagogastric myotomy for achalasia: successful esophageal preservation. *Surg Endosc*. 2016;30:1754-1761. doi:10.1007/s00464-015-4423-3
75. Zhang XC, Li QL, Xu MD, et al. Major perioperative adverse events of peroral endoscopic myotomy: a systematic 5-year analysis. *Endoscopy*. 2016;48:967-978. doi:10.1055/s-0042-110397
76. Haito-Chavez Y, Inoue H, Beard KW, et al. Comprehensive analysis of adverse events associated with per oral endoscopic myotomy in 1826 patients: an international multicenter study. *Am J Gastroenterol*. 2017;112:1267-1276. doi:10.1038/ajg.2017.139
77. Akintoye E, Kumar N, Obaitan I, Alayo QA, Thompson CC. Peroral endoscopic myotomy: a meta-analysis. *Endoscopy*. 2016;48:1059-1068. doi:10.1055/s-0042-114426
78. Lee BH, Shim KY, Hong SJ, et al. Peroral endoscopic myotomy for treatment of achalasia: initial results of a korean study. *Clin Endosc*. 2013;46:161-167. doi:10.5946/ce.2013.46.2.161
79. Li QL, Chen WF, Zhou PH, et al. Peroral endoscopic myotomy for the treatment of achalasia: a clinical comparative study of endoscopic full-thickness and circular muscle myotomy. *J Am Coll Surg*. 2013;217:442-451. doi:10.1016/j.jamcollsurg.2013.04.033
80. Bechara R, Ikeda H, Inoue H. Peroral endoscopic myotomy: an evolving treatment for achalasia. *Nat Rev Gastroenterol Hepatol*. 2015;12:410-426. doi:10.1038/nrgastro.2015.87
81. Ramchandani M, Reddy DN, Darisetty S, et al. Peroral endoscopic myotomy for achalasia cardia: treatment analysis and follow up of over 200 consecutive patients at a single center. *Dig Endosc*. 2016;28:19-26. doi:10.1111/den.12495
82. Ngamruengphong S, Inoue H, Chiu PW, et al. Long-term outcomes of per-oral endoscopic myotomy in patients with achalasia with a minimum follow-up of 2 years: an international multicenter study. *Gastrointest Endosc*. 2017;85:927-933.e2. doi:10.1016/j.gie.2016.09.017
83. Guo H, Yang H, Zhang X, et al. Long-term outcomes of peroral endoscopic myotomy for patients with achalasia: a retrospective single-center study. *Dis Esophagus*. 2017;30:1-6. doi:10.1093/dote/dow011
84. Teitelbaum EN, Dunst CM, Reavis KM, et al. Clinical outcomes five years after POEM for treatment of primary esophageal motility disorders. *Surg Endosc*. 2018;32:421-427. doi:10.1007/s00464-017-5699-2

85. Sharata AM, Dunst CM, Pescarus R, et al. Peroral endoscopic myotomy (POEM) for esophageal primary motility disorders: analysis of 100 consecutive patients. *J Gastrointest Surg*. 2015;19:161-170; discussion 170. doi:10.1007/s11605-014-2610-5
86. Duan T, Zhou J, Tan Y, Liu D. 180 PerOral endoscopic myotomy for severe achalasia: the comparison of full-thickness myotomy and circular myotomy. *Gastrointest Endosc Clin N Am*. 2015;81:AB118.
87. Inoue H, Sato H, Ikeda H, et al. Per-oral endoscopic myotomy: a series of 500 patients. *J Am Coll Surg*. 2015;221:256-264. doi:10.1016/j.jamcollsurg.2015.03.057
88. Hungness ES, Sternbach JM, Teitelbaum EN, Kahrilas PJ, Pandolfino JE, Soper NJ. Per-oral endoscopic myotomy (POEM) after the learning curve: durable long-term results with a Low complication rate. *Ann Surg*. 2016;264:508-517. doi:10.1097/SLA.0000000000001870
89. Nabi Z, Ramchandani M, Chavan R, et al. Per-oral endoscopic myotomy for achalasia cardia: outcomes in over 400 consecutive patients. *Endosc Int Open*. 2017;5:E331-E339. doi:10.1055/s-0043-105517
90. Li QL, Wu QN, Zhang XC, et al. Outcomes of per-oral endoscopic myotomy for treatment of esophageal achalasia with a median follow-up of 49 months. *Gastrointest Endosc*. 2018;87:1405-1412.e3. doi:10.1016/j.gie.2017.10.031
91. Werner YB, Hakanson B, Martinek J, et al. Endoscopic or surgical myotomy in patients with idiopathic achalasia. *N Engl J Med*. 2019;381:2219-2229. doi:10.1056/NEJMoa1905380
92. Shiwaku H, Inoue H, Onimaru M, et al. Multicenter collaborative retrospective evaluation of peroral endoscopic myotomy for esophageal achalasia: analysis of data from more than 1300 patients at eight facilities in Japan. *Surg Endosc*. 2020;34:464-468. doi:10.1007/s00464-019-06833-8
93. McKay SC, Dunst CM, Sharata AM, et al. POEM: clinical outcomes beyond 5 years. *Surg Endosc*. 2021;35:5709-5716. doi:10.1007/s00464-020-08031-3
94. Werner YB, Costamagna G, Swanström LL, et al. Clinical response to peroral endoscopic myotomy in patients with idiopathic achalasia at a minimum follow-up of 2 years. *Gut*. 2016;65:899-906. doi:10.1136/gutjnl-2014-308649
95. Ngamruengphong S, Inoue H, Ujiki MB, et al. Efficacy and safety of peroral endoscopic myotomy for treatment of achalasia after failed Heller myotomy. *Clin Gastroenterol Hepatol*. 2017;15:1531-1537.e3. doi:10.1016/j.cgh.2017.01.031
96. Vigneswaran Y, Yetasook AK, Zhao JC, Denham W, Linn JG, Ujiki MB. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. *J Gastrointest Surg*. 2014;18:1071-1076. doi:10.1007/s11605-014-2496-2
97. Zhou PH, Li QL, Yao LQ, et al. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. *Endoscopy*. 2013;45:161-166. doi:10.1055/s-0032-1326203
98. Onimaru M, Inoue H, Ikeda H, et al. Peroral endoscopic myotomy is a viable option for failed surgical Esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. *J Am Coll Surg*. 2013;217:598-605. doi:10.1016/j.jamcollsurg.2013.05.025
99. Bechara R, Onimaru M, Ikeda H, Inoue H. Per-oral endoscopic myotomy, 1000 cases later: pearls, pitfalls, and practical considerations. *Gastrointest Endosc*. 2016;84:330-338. doi:10.1016/j.gie.2016.03.1469
100. Stavropoulos SN, Modayil RJ, Brathwaite C, et al. 397 anterior vs posterior PerOral endoscopic myotomy (POEM): is there a difference in outcomes? *Gastrointest Endosc*. 2016;83:AB145.
101. Ramchandani M, Nabi Z, Reddy D, et al. Outcomes of anterior myotomy versus posterior myotomy during POEM: a randomized pilot study. *Endosc Int Open*. 2018;6:E190-E198. doi:10.1055/s-0043-121877
102. Tan Y, Lv L, Wang X, et al. Efficacy of anterior versus posterior per-oral endoscopic myotomy for treating achalasia: a randomized, prospective study. *Gastrointest Endosc*. 2018;88:46-54. doi:10.1016/j.gie.2018.03.009
103. Khashab MA, Sanaei O, Rivory J, et al. Peroral endoscopic myotomy: anterior versus posterior approach: a randomized single-blinded clinical trial. *Gastrointest Endosc*. 2020;91:288-297.e7. doi:10.1016/j.gie.2019.07.034
104. Ichkhanian Y, Abimansour JP, Pioche M, et al. Outcomes of anterior versus posterior peroral endoscopic myotomy 2 years post-procedure: prospective follow-up results from a randomized clinical trial. *Endoscopy*. 2021;53:462-468. doi:10.1055/a-1204-4242
105. Rodríguez de Santiago E, Mohammed N, Manolakis A, Shimamura Y, Onimaru M, Inoue H. Anterior versus posterior myotomy during poem for the treatment of achalasia: systematic review and meta-analysis of randomized clinical trials. *J Gastrointestin Liver Dis*. 2019;28:107-115. doi:10.15403/jgld.2014.1121.281.pom
106. Mohan BP, Ofosu A, Chandan S, et al. Anterior versus posterior approach in peroral endoscopic myotomy (POEM): a systematic review and meta-analysis. *Endoscopy*. 2020;52:251-258. doi:10.1055/a-1090-0788
107. Li Q-L, Wu QN, Zhang XC, et al. Outcomes of per-oral endoscopic myotomy for treatment of esophageal achalasia with a median follow-up of 49 months. *Gastrointest Endosc*. 2017;87:1405-1412.e3. doi:10.1016/j.gie.2017.10.031
108. Wang XH, Tan YY, Zhu HY, Li CJ, Liu DL. Full-thickness myotomy is associated with higher rate of postoperative gastroesophageal reflux disease. *World J Gastroenterol*. 2016;22:9419-9426. doi:10.3748/wjg.v22.i42.9419
109. Lu B, Li M, Hu Y, Xu Y, Zhang S, Cai LJ. Effect of peroral esophageal myotomy for achalasia treatment: a Chinese study. *World J Gastroenterol*. 2015;21:5622-5629. doi:10.3748/wjg.v21.i18.5622
110. Jones EL, Meara MP, Schwartz JS, Hazey JW, Perry KA. Gastroesophageal reflux symptoms do not correlate with objective pH testing after peroral endoscopic myotomy. *Surg Endosc*. 2016;30:947-952. doi:10.1007/s00464-015-4321-8
111. Repici A, Fuccio L, Maselli R, et al. GERD after per-oral endoscopic myotomy as compared with Heller's myotomy with fundoplication: a systematic review with meta-analysis. *Gastrointest Endosc*. 2018;87:934-943.e18. doi:10.1016/j.gie.2017.10.022
112. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon consensus. *Gut*. 2018;67:1351-1362. doi:10.1136/gutjnl-2017-314722
113. Bechara R, Inoue H, Shimamura Y, Reed D. Gastroesophageal reflux disease after peroral endoscopic myotomy: lest we forget what we already know. *Dis Esophagus*. 2020;32:doz106. doi:10.1093/dote/doz106
114. Su B, Callahan ZM, Novak S, Kuchta K, Ujiki MB. Using impedance planimetry (EndoFLIP) to evaluate myotomy and predict outcomes after surgery for achalasia. *J Gastrointest Surg*. 2020;24:964-971. doi:10.1007/s11605-020-04513-w
115. Attaar M, Su B, Wong HJ, et al. Intraoperative impedance planimetry (EndoFLIP) results and development of esophagitis in patients undergoing peroral endoscopic myotomy (POEM). *Surg Endosc*. 2021;35:4555-4562. doi:10.1007/s00464-020-07876-y
116. Holmstrom AL, Campagna RAJ, Cirera A, et al. Intraoperative use of FLIP is associated with clinical success following POEM for achalasia. *Surg Endosc*. 2021;35:3090-3096. doi:10.1007/s00464-020-07739-6
117. Moreto M, Ojembarrena E, Barturen A, Casado I. Treatment of achalasia by injection of sclerosant substances: a long-term report. *Dig Dis Sci*. 2013;58:788-796. doi:10.1007/s10620-012-2476-x
118. Mikaeli J, Veisari AK, Fazlollahi N, et al. Ethanolamine oleate versus botulinum toxin in the treatment of idiopathic achalasia. *Ann Gastroenterol*. 2015;28:229-235.

119. Cheng YS, Ma F, Li YD, et al. Temporary self-expanding metallic stents for achalasia: a prospective study with a long-term follow-up. *World J Gastroenterol*. 2010;16:5111-5117. doi:10.3748/wjg.v16.i40.5111
120. Zeng Y, Dai YM, Wan XJ. Clinical remission following endoscopic placement of retrievable, fully covered metal stents in patients with esophageal achalasia. *Dis Esophagus*. 2014;27:103-108. doi:10.1111/dote.12083
121. Aiolfi A, Asti E, Bonitta G, Bonavina L. Esophagectomy for end-stage achalasia: systematic review and meta-analysis. *World J Surg*. 2018;42:1469-1476. doi:10.1007/s00268-017-4298-7
122. Zaninotto G, Annese V, Costantini M, et al. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Ann Surg*. 2004;239:364-370. doi:10.1097/01.sla.0000114217.52941.c5
123. Cheng JW, Li Y, Xing WQ, Lv HW, Wang HR. Laparoscopic Heller myotomy is not superior to pneumatic dilation in the management of primary achalasia: conclusions of a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2017;96:e5525. doi:10.1097/md.0000000000005525
124. Kostic S, Kjellin A, Ruth M, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. *World J Surg*. 2007;31:470-478. doi:10.1007/s00268-006-0600-9
125. Borges AA, Lemme EMO, Abrahao LJ Jr, et al. Pneumatic dilation versus laparoscopic Heller myotomy for the treatment of achalasia: variables related to a good response. *Dis Esophagus*. 2014;27:18-23. doi:10.1111/dote.12064
126. Persson J, Johnsson E, Kostic S, Lundell L, Smedh U. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. *World J Surg*. 2015;39:713-720. doi:10.1007/s00268-014-2869-4
127. Hamdy E, el Nakeeb A, el Hanfy E, et al. Comparative study between laparoscopic Heller myotomy versus pneumatic dilatation for treatment of early achalasia: a prospective randomized study. *J Laparoendosc Adv Surg Tech A*. 2015;25:460-464. doi:10.1089/lap.2014.0682
128. Ponds FA, Fockens P, Lei A, et al. Effect of peroral endoscopic myotomy vs pneumatic dilation on symptom severity and treatment outcomes among treatment-naive patients with achalasia: a randomized clinical trial. *JAMA*. 2019;322:134-144. doi:10.1001/jama.2019.8859
129. Costantini A, Familiari P, Costantini M, et al. Poem versus laparoscopic Heller myotomy in the treatment of esophageal achalasia: a case-control study from two high volume centers using the propensity score. *J Gastrointest Surg*. 2020;24:505-515. doi:10.1007/s11605-019-04465-w
130. Kohn GP, Dirks RC, Ansari MT, et al. SAGES guidelines for the use of peroral endoscopic myotomy (POEM) for the treatment of achalasia. *Surg Endosc*. 2021;35:1931-1948. doi:10.1007/s00464-020-08282-0
131. Dirks RC, Kohn GP, Slater B, et al. Is peroral endoscopic myotomy (POEM) more effective than pneumatic dilation and Heller myotomy? A systematic review and meta-analysis. *Surg Endosc*. 2021;35:1949-1962. doi:10.1007/s00464-021-08353-w
132. de Heer J, Desai M, Boeckxstaens G, et al. Pneumatic balloon dilatation versus laparoscopic Heller myotomy for achalasia: a failed attempt at meta-analysis. *Surg Endosc*. 2021;35:602-611. doi:10.1007/s00464-020-07421-x
133. Karanicolas PJ, Smith SE, Inculet RI, et al. The cost of laparoscopic myotomy versus pneumatic dilatation for esophageal achalasia. *Surg Endosc*. 2007;21:1198-1206. doi:10.1007/s00464-007-9364-z
134. Moonen A, Busch O, Costantini M, et al. Economic evaluation of the randomized European Achalasia trial comparing pneumodilation with laparoscopic Heller myotomy. *Neurogastroenterol Motil*. 2017;29:e13115. doi:10.1111/nmo.13115
135. Greenleaf EK, Winder JS, Hollenbeak CS, Haluck RS, Mathew A, Pauli EM. Cost-effectiveness of per oral endoscopic myotomy relative to laparoscopic Heller myotomy for the treatment of achalasia. *Surg Endosc*. 2018;32:39-45. doi:10.1007/s00464-017-5629-3
136. Attaar M, Su B, Wong HJ, et al. Comparing cost and outcomes between peroral endoscopic myotomy and laparoscopic heller myotomy. *Am J Surg*. 2021;222:208-213. doi:10.1016/j.amjsurg.2020.10.037
137. Conte TM, Haddad LBP, Ribeiro IB, de Moura ETH, D'Albuquerque L, de Moura EGH. Peroral endoscopic myotomy (POEM) is more cost-effective than laparoscopic Heller myotomy in the short term for achalasia: economic evaluation from a randomized controlled trial. *Endosc Int Open*. 2020;8:E1673-E1680. doi:10.1055/a-1261-3417
138. Khan MA, Kumbhari V, Ngamruengphong S, et al. Is POEM the answer for management of spastic esophageal disorders? A systematic review and meta-analysis. *Dig Dis Sci*. 2017;62:35-44. doi:10.1007/s10620-016-4373-1
139. Werner YB, Rösch T. Endoscopic or surgical myotomy in achalasia. Reply. *N Engl J Med*. 2020;382:1377-1378. doi:10.1056/NEJMc2000065

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rolland S, Paterson W, Bechara R. Achalasia: Current therapeutic options. *Neurogastroenterology & Motility*. 2022;00:e14459. doi: 10.1111/nmo.14459