Management of treatment-naïve achalasia: choosing the right therapeutic option

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Abstract: Achalasia is the most common motility disorder of the oesophagus. This condition, characterized by failed relaxation of the lower esophageal sphincter (LES) and absence of peristalsis results in progressive dysphagia to both solids and liquids, leading to malnutrition and poor quality-of-life. There is currently no cure for achalasia with available treatments aimed at symptomatic palliation through reducing LES pressure. The therapeutic landscape for achalasia is dynamic and evolving, with treatment options ranging from medical (nitric oxide donors and calcium channel blockers), endoscopic [botulinum toxin injection, pneumatic balloon dilatation, stenting, and peroral endoscopic myotomy (POEM)], to surgery (Heller's cardiomyotomy and oesophagectomy). Here, we will review the different therapeutic options for achalasia, and discuss the important factors to consider when tailoring the right treatment modality for patients with treatment-naïve disease.

Keywords: Achalasia; treatment; dilatation; peroral endoscopic myotomy (POEM); cardiomyotomy

Introduction

Achalasia is a chronic and progressive motility disorder of the esophagus characterized by failure of the lower esophageal sphincter (LES) to relax after swallowing (1). This is associated with aperistalsis and intraluminal pressurization along the esophageal body (2). Together they impair the transit of food from the mouth into the stomach, resulting in gradual onset dysphagia to both solids and liquids. Other symptoms may include regurgitation, chest pain, coughing and weight loss (1). Additionally, patients are at risk of aspiration pneumonia, malnutrition, and esophageal squamous cell carcinoma (3).

Achalasia is an uncommon disease. In the era of high-resolution manometry (HRM), the estimated incidence is 2–3/100,000 persons/year with a prevalence of 1/10,000 (4-6). Although the incidence increases with age, it does not discriminate between gender or race (7-9).

The etiology of achalasia is not well understood, but is likely multifactorial with infection, autoimmunity and neurodegeneration as contributing factors (10,11). The most common form of achalasia is idiopathic, where there is selective loss of nitric oxide and vasoactive intestinal peptide producing inhibitory neurons within the myenteric plexus of Auerbark (10-12). This leads to unopposed vagal acetylcholine stimulation of the LES and esophageal smooth muscles, resulting in aperistalsis, intraluminal pressurization, and impaired esophageal emptying (13). A similar clinical picture can be seen in patients with proximal gastric cancers (pseudo-achalasia) or Chagas disease, whereby the myenteric plexus is destroyed by tumor infiltration or *Trypanosoma cruzi* infection, respectively (14,15).

The diagnosis of achalasia is based on a combination of radiologic, manometric, and endoscopic findings. The timed barium esophagram, although operator dependent, is diagnostic in over 80% of cases (16). Pathognomonic findings on barium swallow include the "bird's beak" appearance at the gastro-esophageal junction (GEJ),

dilated esophageal body, aperistalsis, and a barium height of >2 cm at five minutes (17). HRM demonstrates impaired LES relaxation (18), classifies achalasia into three distinct subtypes, and excludes other functional disorders of the esophagus (19). Importantly, upper gastrointestinal endoscopy is required to rule out pseudo-achalasia (20).

This review will focus on the management of idiopathic achalasia. Here, we will discuss the aims of treatment, therapeutic options, their mechanisms of action and clinical outcomes, as well as some pertinent factors to consider when selecting the right treatment modality for patients with treatment-naïve disease.

Treatment objectives in achalasia

There is currently no cure for achalasia. Treatment options are aimed at symptomatic palliation, particularly of dysphagia and regurgitation, to improve quality-of-life (21).

Treatment options and their therapeutic mechanisms

Current therapies for achalasia are aimed at reducing LES pressure (22). This can be accomplished pharmacologically using muscle relaxants or mechanically by dividing muscle fibers. Therapeutic strategies can also be categorized into medical, endoscopic, and surgical modalities.

Medicinal agents include nitric oxide donors (sildenafil and nitrates) and the calcium channel blocker, nifedipine. Glyceryl trinitrate or isosorbide dinitrate are prodrugs which undergo enzymatic metabolism to produce nitric oxide. This metabolite, via intracellular signaling, relaxes smooth muscles (23). Sildenafil potentiates the same pathway by inhibiting phosphodiesterase-mediated degradation of nitric oxide (24). Contrastingly, nifedipine interferes with calcium influx into smooth muscle cells by blocking transmembrane calcium channels, thereby preventing muscle contraction (25). Through these mechanisms, nitrates, sildenafil and nifedipine relaxes the LES. However, as these agents act systemically, they have dose-limiting adverse effects (26).

Endoscopic therapies for achalasia include *botulinum* toxin (botox) injection, pneumatic balloon dilatation, peroral endoscopic myotomy (POEM), and placement of a self-expanding metallic stent (SEMS). For botox injection, approximately 80–100 units of *botulinum* toxin is injected into four quadrants of the LES (27). Botox acts by binding presynaptically to high-affinity recognition sites on vagal nerve terminals to decrease acetylcholine

release. This causes a neuromuscular blockade leading to relaxation of the LES (28). The effect of botox typically last for 3–12 months (27). Pneumatic balloon dilatation involves stretching and subsequently breaking the LES muscle fibers through the use of a 10 cm long and 30–40 mm diameter high pressure balloon (21). Dilatation can be once-off or undertaken in a graded fashion titrated to the patient's symptoms. POEM is an advanced endoscopic technique involving division of the inner circular muscle fibers of the distal oesophagus, LES, and gastric cardia through an endoscopically created submucosal tunnel (29). Stenting has been recently proposed as another therapeutic strategy for achalasia. This technique aims to deploy a retrievable 5–10 cm long and 20–30 mm wide, partially or fully covered SEMS across the GEJ to maintain its patency (30).

Surgery for achalasia is an esophago-cardiomyotomy or Heller's myotomy, whereby the serosal and muscular layers of the distal oesophagus, GEJ, and gastric cardia are divided. The myotomy usually extends 6-8 cm along the anterior surface of the esophagus and 2–3 cm along the lesser curve of the stomach (31-34). This operation is commonly laparoscopic, and incorporates a partial fundoplication to minimize postoperative gastroesophageal reflux (35).

Whilst the plethora of options listed above have all been described, the mainstay of treatment is by and large limited to surgical myotomy, balloon dilation and in palliative cases, botox injection. POEM is increasingly finding favor as an alternative to surgical myotomy but is early in evolution of long-term results.

Treatment considerations

Given the range of treatment options available for achalasia, the choice of intervention should take into account patient, disease, procedural, and surgeon factors. Patient factors include their age, frailty, active co-morbidities, symptomatology, previous esophago-gastric and hiatal surgery, as well as personal preferences. Disease factors include objective measurements of disease severity, underlying esophageal anatomy, achalasia subtype, and whether the patient has presented with treatment-naïve, recurrent or end-stage disease. Procedural factors include the likelihood of achieving technical success and long-term symptomatic remission. This needs to be balanced against the potential adverse outcomes of each intervention. Finally, surgeon expertise and institutional resources may also influence clinical decision making. In the literature,

the definition of therapeutic success is variably reported. Outcomes may be assessed using symptoms scores (e.g., Eckardt score) and quality-of-life questionnaires (e.g., SF-36), or determined using radiologic and manometric investigations. Not infrequently however, motility parameters fail to correlate with clinical response to treatment (21).

Therapies for treatment-naïve achalasia

Medical therapy

Muscle relaxants reduce LES pressure and increase esophageal emptying (36-43). However, their symptomatic control is rather disappointing (44), and does not correlate with objective testing (37,45,46). Additionally, common side-effects such as headaches, postural hypotension, tachyphylaxis, and peripheral edema result in poor compliance. Critically, the quality of evidence supporting their use is poor. Existing trials are improperly designed, lack power, and have no long-term follow-up. In a Cochrane review by Wen *et al.*, only two randomized controlled trials (RCT) of nitrates for achalasia were identified. The authors concluded that these studies were inappropriately designed and therefore had no implications on practice (47). Similarly, a systematic review by Bassotti *et al.* found that there were limited data to demonstrate the effectiveness of nifedipine, nitrates, and sildenafil for patients with achalasia (48). Therefore, in light of poor-quality evidence, limited clinical efficacy, and dose-limiting adverse outcomes, muscle relaxants are currently not recommended for the treatment of achalasia (21).

SEMS

SEMS have been recently proposed as a potential therapeutic strategy for achalasia. They are typically removed 5–6 days after deployment. Experience with SEMS is predominantly limited to several Chinese groups (49-55), with only three case series totaling 26 patients reported from European investigators (56-58). Overall, technical success as defined by adequate stent deployment and immediate symptomatic control was achieved in all patients. Clinical remission at three years post-intervention ranged from 49–85% (51-53,56,59), with one prospective non-randomized study reporting a durable long-term remission rate of 83% at ten years (54,55). This study also compared SEMS with pneumatic balloon dilatation and found that SEMS had superior long-term dysphagic control (SEMS 78% *vs.* pneumatic balloon dilatation 17%). Similarly, in an RCT

of SEMS versus botox injection, SEMS achieved greater symptomatic response (SEMS 49% *vs.* botox 4%) and lower sphincteric pressures than botox injection at three years post-intervention (53). Despite these encouraging results, patients who received SEMS experienced significantly higher complications than those who underwent pneumatic balloon dilatation or botox injection (53,55). These included bleeding 12% (50,54), chest pain 25–40% (50,54), gastro-esophageal reflux 20% (50,54) and stent migration 5–10% (54), including one case of colonic obstruction by SEMS migration (56). Importantly, the efficacy of SEMS was inconsistent across different studies. For example, in a retrospective analysis by Zhao *et al.*, SEMS and pneumatic balloon dilatation achieved comparable remission rates (SEMS 47% *vs.* pneumatic balloon dilatation 53%) at three years (51). Taken together, due to limited global experience and variable efficacy, there is currently insufficient evidence to support the general use of retrievable SEMS for patients with achalasia (60). Certainly, the authors would caution against this strategy.

Botulinum toxin (Botox) injection

Botox was first proposed as a treatment option for achalasia over 20 years ago (61). Despite its modest clinical efficacy, botox injection is still used today owing to a very high safety profile. On the basis of symptomatic, radiologic and manometric assessment, botox injection has an overall technical failure rate of 10–35% due to inadequate dosing and misplaced injections (62-66). In patients who respond to botox therapy, symptomatic control typically lasts for 3–12 months after the first injection (66-68), and 8–16 months after the second injection (66,68,69). Clinical response is associated with a 30–40% reduction in mean sphincteric pressure (70), but it is unclear whether treatments beyond the second injection further extends the clinical remission period. Botox injection is generally well tolerated with commonly described adverse effects including chest discomfort and gastro-esophageal reflux in 5–20% of patients. Rarely, bleeding, mucosal ulceration, mediastinitis, and allergic reactions can occur.

Several RCTs have compared the outcomes of botox injection to pneumatic balloon dilatation and laparoscopic Heller's myotomy (*Table 1*) (53,62,63,65,71-74). Compared to pneumatic balloon dilatation, botox injection achieved equivalent symptomatic control at six months post-intervention. However by one year, disease recurrence was significantly higher in the botox injection cohort (63,65,69,71,72,75). A Cochrane meta-analysis of five

Table 1 Randomized controlled trials of botox injection versus other therapies

Author, year	Comparator cohort	Study size	Technical success (%)	Follow up (year)	Symptoms score reduction	Oesophageal, retention	LOS, pressure reduction	Clinical remission
Bansal, 2003 (62)	RCT, BTI vs. PD	BTI: N=16 PD: N=18	BTI: 75 PD: 89	1	NS	NR	NS	BTI: 38% vs. PD: 89%, P<0.001
Vaezi, 1999 (71)	RCT, BTI vs. PD	BTI: N=22 PD: N=20	BTI: 73 PD: 70	1	PD > BTI, P<0.001	PD < BTI, P<0.001	PD > BTI, P<0.001	BTI: 32% vs. PD: 70%, P=0.01
Ghoshal, 2001 (65)	RCT, BTI vs. PD	BTI: N=7 PD: N=10	BTI: 86 PD: 80	1	NR	NR	NR	BTI: 29% vs. PD: 75%, P=0.027
Mikaeli, 2001 (72)	RCT, BTI vs. PD	BTI: N=40 PD: N=40	BTI: 98 PD: 98	1	NR	NR	NR	BTI: 15% vs. PD: 53%, P<0.001
Muehldorfer, 1999 (63)	RCT, BTI vs. PD	BTI: N=12 PD: N=10	BTI: 75 PD: 83	2.5	PD > BTI, P<0.05	NR	NR	BTI: 0% vs. PD: 60%, P<0.05
Zhu, 2009 (73)	RCT, BTI vs. PD vs. PD + BTI	BTI: N=30 PD: N=30 PD + BTI: N=30	NR	2	PD + BTI > BTI or PD, P<0.05	NR	PD + BTI > BTI or PD, P<0.05	BTI: 14% vs. PD: 36% vs. PD + BTI: 57%, P<0.05
Zaninotto, 2004 (74)	RCT, BTI vs. LHM	BTI: N=40 LHM: N=40	NR	2	LHM > BTI, P<0.05	LHM < BTI, P<0.05	NS	BTI: 35% vs. PD: 88%, P<0.05
Cai, 2013 (53)	RCT BTI vs. SEMS	BTI: =51 SEM: 59	BTI: 94 SEM: 100	3	SEM > BTI, P<0.05	NR	SEM > BTI, P<0.05	BTI: 4% vs. SEM: 49%, P<0.01

LOS, lower oesophageal sphincter; RCT, randomised controlled trial; BTI, Botulinum toxin injection; PD, pneumatic dilatation; LHM, laparoscopic Heller's myotomy; SEMS, self-expanding metal stents; NS, not significant; NR, not recorded; LOS pressure, measured by manometry. Retention, measured by nuclear scintigraphy or barium swallow.

RCTs found that despite similar clinical and manometric outcomes between pneumatic balloon dilatation and botox injection at one month post-treatment, remissions rates were significantly lower at 6 (Pneumatic balloon dilatation 81% vs. Botox injection 52%, RR: 1.57, 95% CI: 1.19–2.09) and 12 (Pneumatic balloon dilatation 73% vs. Botox injection 38%, RR: 1.88, 95% CI: 1.35–2.61) months in patients who received botox injection. Complication rates were comparable between the two groups, however, three cases of esophageal perforation were identified in the pneumatic balloon dilatation cohort (76). Similarly, whilst symptom control and sphincteric pressures were comparable between botox injection and laparoscopic Heller's myotomy at six months post-intervention, disease remission was significantly higher in patients who underwent laparoscopic Heller's myotomy than botox injection at two years (77). The efficacy of combining botox injection with pneumatic balloon dilatation has also been evaluated in three prospective trials (66,73,78). Combination botox injection and pneumatic balloon dilatation achieved greater symptomatic response, lower sphincteric pressures, and longer disease remission than single modality therapy across all studies.

Numerous studies have sought to identify predictors of therapeutic response to botox injection. Amongst the many factors that have been evaluated, older age (>50 years) and a low baseline sphincteric pressure (<40 mmHg) are favorable predictors of response and durability (64,66,79,80). Although not validated across all studies (72,77), younger patients are associated with higher rates of complications from botox injection (81). Based on these findings, botox injection may be recommended as first line therapy for achalasia in patients over 50 years of age, with low baseline sphincter pressures, who are co-morbid and unfit for other more invasive therapies (pneumatic balloon dilatation, laparoscopic Heller's myotomy, or POEM). Botox injection may also be used in conjunction with pneumatic balloon dilatation to augment treatment response.

Pneumatic balloon dilatation

Pneumatic balloon dilatation was first introduced in the same era as botox injection (82). Overall, technical success as defined by improvement in symptoms scores within the first month post-dilatation, ranges from 75–96% (63,65,67,83-85). Clinical response typically lasts for 10–12 months (78,86) with repeated dilatations lengthening the remission period. In a retrospective analysis by West et al., patients who underwent 3–7 dilatations were found

Table 2 Randomised controlled trial of pneumatic balloon dilatation versus other therapies

Author, year	Comparator cohort	Study size	Technical success (%)	Follow up (year)	Symptoms score reduction	Oesophageal, retention	LOS pressure reduction	Clinical Remission
Moonen, 2016 (95)	RCT PD vs. LHM	PD: N=96 LHM: N=105	NR	5	NS	NS	NS	PD: 82% vs. LHM: 84%, P=0.92
Kostic, 2007 (96)	RCT PD vs. LHM	PD: N=16 LHM: N=25	NR	1	NS	NR	NR	PD: 77% vs. LHM: 92%, P=0.04
Hamdy, 2015 (85)	RCT, PD vs. LHM	PD: N=25 LHM: N=25	PD: 76 LHM: 96	1	NR	NR	LHM >PD, P<0.001	PD: 74% vs. LHM: 92%, P=0.04
Boeckxstaens, 2011 (92)	RCT PD vs. LHM	PD: N=95 LHM: N=106	PD: 96 LHM: 86	2	NS	NS	NS	PD: 85% vs. LHM: 90%, P=0.46
Borges, 2014 (97)	RCT PD vs. LHM	PD: N=46 LHM: N=46	PD: 73 LHM: 84	2	NS	NS	NS	PD: 54% vs. LHM: 60%, P>0.05
Persson, 2015 (98)	RCT PD vs. LHM	PD: N=28 LHM: N=25	NR	5	NS	NR	NR	PD: 64% vs. LHM: 92%, P=0.016
Chrystoja, 2016 (99)	RCT PD vs. LHM	PD: N=25 LHM: N=25	NR	5	NS	NR	NS	NR
Csendes, 1989 (82)	RCT, PD vs. LHM	PD: N=39 LHM: N=42	PD: 49 LHM: 72	5	NR	NR	LHM>PD, P<0.01	PD: 65% vs. LHM: 95%, P<0.01
Ponds, 2019 (90)	RCT PD vs. POEM	PD: N=66 POEM: N=64	PD: 80 POEM: 98	2	NS	POEM>PD, P=0.05	POEM>PD, P=0.07	PD: 54% vs. POEM: 92%, P<0.001

LOS, lower oesophageal sphincter; RCT, randomised controlled trial; BTI, Botulinum toxin injection; PD, pneumatic dilatation; LHM, laparoscopic Heller's myotomy; SEMS, self-expanding metal stents; NS, not significant; NR, not recorded; LOS pressure, measured by manometry. Retention, measured by nuclear scintigraphy or barium swallow.

to have a clinical relapse rate of 60% at 15 years (87). Symptomatic response was associated with a 20–30% decrease in mean sphincteric pressure, and a 30% reduction in esophageal diameter (88). Commonly reported adverse events included chest pain 27% (54), bleeding 5% (54), and gastro-esophageal reflux 5–40% (83,84,88-91). Esophageal perforation occurred in 1-8% of dilatations (83,88,91-95), a major complication potentially resulting in significant patient morbidity. Perforation risk was highest in patients over 65 years of age, with high amplitude distal esophageal contractions, undergoing their first dilatation, and/or using a Witzel dilator (as compared with the Rigiflex balloon from Boston Scientific) (94).

Pneumatic balloon dilatation has been compared to laparoscopic Heller's myotomy in several RCTs (*Table 2*) (82,85,90,92,95-99). At one year post-intervention, patient who underwent laparoscopic Heller's myotomy achieved better symptomatic control than those who were dilated (85,100). This difference however, was not appreciable at two years, with most trials demonstrating comparable remission rates, LES pressures, esophageal emptying times and quality-of-life scores at two, five and six years of follow-

up (95-97,99,101). Only two studies have reported a higher remission rate in the laparoscopic Heller's myotomy group at five years post-intervention (82,102). Similarly, two meta-analyses inferred a relative therapeutic equivalence between pneumatic balloon dilatation and laparoscopic Heller's myotomy in the short to medium term (103,104). Pneumatic balloon dilatation however, is associated with higher rates of gastro-esophageal reflux (82,84,97), and esophageal perforation than laparoscopic Heller's myotomy (95,103,104).

Pond *et al.* compared pneumatic balloon dilatation to POEM in a world-first RCT (90). They found that despite dilating with a 40 mm diameter balloon, remission rates at three, twelve and twenty-four months were inferior to the POEM cohort. POEM also resulted in lower sphincteric pressures and improved esophageal emptying but was associated with a significantly higher rate of gastro-esophageal reflux.

The predictors of therapeutic response to pneumatic balloon dilatation are similar to those identified for botox injection. These include older age (>40 years), type 2 achalasia (Chicago classification v3), and a post-dilatation LES pressure <10 mmHg (105-107). Although not confirmed in all studies (88,108), male gender, daily

chest pain, age <40 years, type 3 achalasia, severely delayed esophageal emptying (on timed barium swallow), and a pre-treatment esophageal diameter <4 cm are potential predictors of treatment failure (92,95).

In summary, pneumatic balloon dilatation may be recommended as first line therapy for achalasia in patients over 40 years of age with type 2 achalasia who decline laparoscopic Heller's myotomy or POEM and accept the risk of esophageal perforation associated with pneumatic balloon dilatation.

POEM

POEM is a relatively novel technique introduced in the last decade for the treatment of achalasia. As a result, outcome data is limited with most reporting single center retrospective series with short to medium term follow-up. Overall, the technical success rate for this procedure, as defined by an Eckardt score ≤3 within three months post-intervention, ranged from 90–100% (90,109-111). Symptomatic relapse at three years was approximately 10–15% (111-113), with a projected median symptom-free interval of five years (112,114). Clinical response to POEM was typically associated with a mean LES pressure reduction of 60–70% (109,112), a decrease in mean barium height of 80% (114), and significant improvements in quality-of-life scores at one year post-intervention (115). The learning curve for POEM is estimated to be 7–40 cases (116-119).

Based on two large systematic reviews, the POEM procedure has a major complication rate of 2.7–3.3% and an overall mortality rate of less than 0.1% (114,120). The potentially life-threatening complications include esophageal perforation and bleeding (109,121) and, although not life-threatening, POEM results in the highest rate of gastro-esophageal reflux amongst all therapies for achalasia (21). As evidenced by pH monitoring, the risk of abnormal esophageal acid exposure has been reported to be as high as 88% after POEM (122). Despite a relatively poor correlation between objective testing and clinical disease (122,123), 10-65% of patients experience symptomatic reflux within one year of POEM (90,109,113,114,121,124,125). The risk of developing gastro-esophageal reflux disease (GERD), along with the severity of reflux, also increases with time (112). Hiatus hernia and obesity have been found to be predictors of GERD development (116), and although most patients responded to proton pump inhibitors, they became dependent on this therapy (122).

Comparative studies between POEM and laparoscopic Heller's myotomy have uniformly demonstrated equivalence in most intraoperative and postoperative domains (110,114,126-132), including operative time, analgesic requirements and complication rates. Functional outcomes such as Eckardt scores, LES pressures, esophageal emptying times, and quality-of-life measures were also comparable between the two modalities. In some studies, POEM was associated with a slightly shorter (<24 h) length of stay (130,133). The risk of GERD however, was markedly higher in the POEM cohort than those who underwent laparoscopic Heller's myotomy (132,134-136). These findings are quantified by a large meta-analysis, which demonstrated that POEM and laparoscopic Heller's myotomy have similar remission rates at one (94% *vs.* 91%) and two (93% *vs.* 90%) years of follow-up. The risk of abnormal esophageal acid exposure (OR 4.3, 95% CI: 2.96–6.27), erosive esophagitis (OR 9.31, 95% CI: 4.71–19.85), and GERD (OR 1.69, 95% CI: 1.33–2.14) were significantly higher in the POEM cohort (137).

Several studies have analyzed potential predictors of therapeutic outcome for POEM. Similar to botox injection and pneumatic balloon dilatation, younger age and type 3 achalasia have been associated with early disease relapse (110,113). These factors however, have not been validated in other studies (109).

In summary, POEM has been validated as a treatment option for achalasia. It achieves excellent outcomes in the short to medium term whilst being less invasive than laparoscopic Heller's myotomy. Given the lack of long-term outcome data, and a relatively higher risk of postoperative GERD, POEM may be most appropriate for older patients, and those with greater co-morbidities (133).

Heller's myotomy

Heller's cardiomyotomy is regarded as the gold standard treatment for achalasia (21). This procedure was initially performed via an open trans-thoracic or trans-hiatal approach (138,139). With advances in minimally invasive technology over the last 30 years, most surgeons have elected to myotomize the esophagus via a laparoscopic trans-hiatal route (139). Overall, this technique has excellent efficacy with a technical success rate, as defined by a decrease in symptoms score within the first three months post laparoscopic Hellers myotomy, ranging from 80–100% in contemporary series (67,84). This is associated with a mean LES pressure reduction of 40–80% (140). Prospective trials have reported a five-year recurrence rate post

laparoscopic Heller's myotomy of approximately 5–15% (82,95). Retrospective studies have demonstrated durable disease control from laparoscopic Heller's myotomy with 20–30% of patients experiencing clinical relapse (141,142). The failure to alleviate dysphagia is partly attributed to inadequate myotomy length (31,33,142). The learning curve for laparoscopic Heller's myotomy is relatively short and is estimated to be 16–20 cases (143,144).

Laparoscopic Heller's myotomy has a high safety profile. In a single center series of 400 patients by Zaninotto *et al.*, their reported morbidity and mortality rates were 2% and 0% respectively (33). Causes of postoperative complications include mucosal perforation, splenic injury, pneumothorax and wound bleeding (33). GERD is the most common long-term adverse outcome following laparoscopic Heller's myotomy (145) and its incidence increases with time (141). In those who have undergone a concurrent fundoplication, 7–15% of patients have abnormal acid exposure on pH monitoring (85,141,146-149). This is associated with a 5–11% risk of erosive esophagitis (149), and 2–7% risk of symptomatic reflux (149-151). Without fundoplication, the rate of symptomatic reflux, as reported by Jara *et al.*, increases from 24% at one year to 48% at ten years post laparoscopic Heller's myotomy (141). Data from RCTs have shown that a partial fundoplication procedure (either anterior 180 or posterior 270 degrees) significantly reduced the risk of GERD post laparoscopic Heller's myotomy (35,152), without compromising the swallowing function of a myotomy (153). There appeared to be no difference in reflux control between a Dor or Toupet fundoplication (154,155). In contrast, Rebecchi *et al.* demonstrated in their RCT that a 360-degree Nissen fundoplication generated more dysphagia without additional reflux control at five years of follow-up (151).

Based on trials highlighted above, laparoscopic Heller's myotomy with fundoplication achieves superior achalasia-related symptomatic control than botox injection, but has similar medium-term efficacy when compared with pneumatic balloon dilatation and POEM. Importantly, in comparison to pneumatic balloon dilatation and POEM, laparoscopic Heller's myotomy with fundoplication has the lowest rate of post-interventional GERD.

The factors that predict therapeutic success post-LHM include: age >40 years, pre-treatment LES pressures >30 mmHg, and post-treatment LES pressures <18 mmHg or a >50% decrease in LES pressures (33,97,156). Conversely, the factors that predict treatment failure include male gender, daily chest pain, severe preoperative dysphagia, sigmoid esophagus, and type 3 achalasia (33, 150).

Taken together, laparoscopic Heller's myotomy with fundoplication is the current standard of care for patients with achalasia. This procedure should be recommended to patients who are young, fit for surgery, with high baseline LES pressures, and who are not prepared to accept the higher risk of GERD that is associated with pneumatic balloon dilatation and POEM.

Therapies for different subtypes of achalasia

The advent of HRM has enabled the reclassification of achalasia into three distinct subtypes (19). As detailed in the Chicago Classification version 3.0 (157), type 1 achalasia is characterized by aperistalsis without abnormal esophageal pressures, type 2 features aperistalsis with intermittent periods of pan-esophageal pressurization, and type 3 is defined as aperistalsis with distal esophageal spastic contractions (27). Type 2 is the most prevalent, accounting for 65% of all presentations. Types 1 and 3 constitutes the remaining 25% and 10%, respectively (158). Importantly, these subtypes predict therapeutic outcomes (159). Type 2 achalasia exhibit the greatest response to botox injection, pneumatic balloon dilatation, laparoscopic Heller's myotomy and POEM (96–100%). This is followed by types 1 (56–81%) and 3 (29–66%) (19,116). A meta-analysis of non-randomized studies supports these findings (160). Furthermore, disease recurrence is lowest in type 2 and highest in type 3 achalasia (27,158). In a series of 246 consecutive patients, Salvador *et al.* found that clinical relapse at six months post laparoscopic Heller's myotomy was 5%, 15% and 30% for subtypes 2, 1 and 3, respectively (161).

Currently, there is insufficient evidence to enable personalized therapy based on HRM alone. There are no trials that specifically compare the efficacy of botox injection across different achalasia subtypes. In a post-hoc analysis of a multicenter European trial which randomized patients to pneumatic balloon dilatation or laparoscopic Heller's myotomy, Rohof *et al.* found that at two years post-treatment, pneumatic balloon dilatation achieved greater symptomatic control than laparoscopic Heller's myotomy in those with type 2 achalasia (158). This difference, despite being statistically significant, was small in effect (pneumatic balloon dilatation 100% *vs.* laparoscopic Heller's myotomy 93%). In the same analysis, laparoscopic Heller's myotomy had a higher success rate than pneumatic balloon dilatation for patients with type 3 achalasia (laparoscopic Heller's myotomy 86% *vs.* pneumatic balloon dilatation 40%). However, this comparison failed to reach statistical

Table 3 Factors to consider when choosing the right therapy for treatment-naïve achalasia

Therapeutic modality	Patient factors	Disease factors	Procedural factors	Surgeon factors	Recommendations
Muscle relaxant	NA	NA	NA	NA	Not recommended
Self-expanding metallic stents	NA	NA	NA	NA	Not recommended outside of clinical trials
Botox injection	• Age >50 years	• Type 2 achalasia	• Accepts likelihood of repeated treatments	NA	Consider 1st line treatment
	• Frail	• Baseline LES pressure <40 mmHg	• Does not accept perforation risk		
	• Co-morbid				
	• Decline more invasive treatments				
Pneumatic balloon dilatation	• Age >50 years	• Type 2 achalasia	• Accepts likelihood of repeated treatments	• Available expertise	Consider 1st line treatment
	• Co-morbid		• Accepts 1–8% risk of perforation	• Available achalasia balloon	
	• Previous hiatal surgery		• Accepts 5–40% risk of GERD		
	• Decline more invasive treatments				
Peroral endoscopic myotomy	• Co-morbid	• Type 2 achalasia	• Accepts up to 60% risk of GERD	• Available expertise	Consider in those who decline Heller's myotomy and accepts GERD risk
	• Previous hiatal surgery	• Potentially type 3 achalasia			
	• Decline Heller's myotomy				
Laparoscopic Heller's myotomy and partial fundoplication	• Fit for laparoscopic surgery	• Any achalasia type	• Prioritize GERD control	• Available expertise	Consider 1st line treatment

LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease; NA, not applicable.

significance due to low patient numbers (158).

Laparoscopic Heller's myotomy is the current gold standard for the treatment of type 3 achalasia. However, POEM is conceivably superior as it allows for a longer myotomy. Despite a paucity of studies in this area, available data suggests that POEM is effective for patients with type 3 achalasia. Reported disease remission rates at 19, 27 and 40 months post-POEM are 90% (116), 89% (126), and 87% (113) respectively. In a retrospective study comparing POEM to laparoscopic Heller's myotomy in patients with type 3 achalasia, POEM achieved significantly higher clinical response (POEM 98% *vs.* laparoscopic Heller's myotomy 81%), shorter operative time (median, POEM: 102 min *vs.* laparoscopic Heller's myotomy 264 min), longer myotomy length (median, POEM 16 cm *vs.* laparoscopic Heller's myotomy 8 cm), and lower perioperative adverse events (162).

In summary, manometric subtypes of achalasia have prognostic value. Type 2 predicts favorable response and type 3 is associated with disease recurrence for all treatment modalities. Laparoscopic Heller's myotomy, pneumatic balloon dilatation and POEM have similar efficacy for types 1 and 2. In type 3 achalasia, laparoscopic Heller's myotomy is potentially more efficacious than pneumatic balloon dilatation, whilst POEM may be an overall superior alternative. Despite these findings, treatment decisions should be holistic and not based solely on HRM classification.

Conclusions

Although an uncommon disease, achalasia is the most well-defined esophageal motility disorder. Multiple

treatment options have been proposed with a wide range of therapeutic efficacies and safety profiles. It is crucial to consider patient, disease, procedural, and surgeon factors (*Table 3*) when tailoring the right therapeutic approach for patients with treatment-naïve disease.

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