Clinical management of achalasia: current state of the art

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Abstract: Achalasia is a primary disorder of esophageal motility. It classically presents with dysphagia to both solids and liquids but may be accompanied by regurgitation and chest pain. The gold standard for the diagnosis of achalasia is esophageal motility testing with manometry, which often reveals aperistalsis of the esophageal body and incomplete lower esophageal sphincter relaxation. The diagnosis is aided by complimentary tests, such as esophagogastroduodenoscopy and contrast radiography. Esophagogastroduodenoscopy is indicated to rule out mimickers of the disease known as “pseudoachalasia” (eg, malignancy). Endoscopic appearance of a dilated esophagus with retained food or saliva and a puckered lower esophageal sphincter should raise suspicion for achalasia. Additionally, barium esophagography may reveal a dilated esophagus with a distal tapering giving it a “bird’s beak” appearance. Multiple therapeutic modalities aid in the management of achalasia, the decision of which depends on operative risk factors. Conventional treatments include medical therapy, botulinum toxin injection, pneumatic dilation, and Heller myotomy. The last two are defined as the most definitive treatment options. New emerging therapies include peroral endoscopic myotomy, placement of self-expanding metallic stents, and endoscopic sclerotherapy.

Keywords: achalasia, pseudoachalasia, pneumatic dilation, Heller myotomy, botulinum toxin injection, peroral endoscopic myotomy

Introduction

Achalasia, a primary esophageal motility disorder, is classically characterized by impaired relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis.¹ The primary pathophysiologic disturbance is the loss of inhibitory interneurons in the myenteric plexus that are involved in facilitating LES relaxation for gastric accommodation of food boluses.² Consequently, the classic symptomatic presentation involves dysphagia to both solids and liquids associated with regurgitation of undigested food. Further associated symptoms include substernal chest pain with dysphagia, weight loss, and dyspepsia that often leads to a misdiagnosis of gastroesophageal reflux disease.^{3,4} The incidence of achalasia is one in 100,000 individuals annually with a prevalence of ten in 10,000. It occurs equally among women and men and is without racial predilection. The peak incidence is between 30 and 60 years of age.^{5,6}

Various diagnostic modalities have been implemented that assist in the diagnosis of achalasia. It is characterized on radiographic barium swallow by aperistalsis resulting in poor emptying of barium, esophageal dilation, and minimal LES opening, resulting in a tapering of the barium column giving it a “bird’s beak” appearance (Figure 1A). Endoscopically, it is characterized by a dilated esophagus with retained

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saliva, undigested food particles, and liquid in the absence of attributing strictures or tumors (Figure 1B). Occasionally, patients are found to have a dilated esophagus when undergoing computed tomography of the chest (Figure 1C). Manometrically, it is characterized by incomplete relaxation of the LES and aperistalsis of the esophageal body (Figure 1D).¹

The options for treatment of achalasia are vast with many new emerging therapies. Although no current treatment option is a definitive cure, the aim is to reduce the hypertonicity of the LES in an effort to relieve symptoms, improve esophageal emptying, and prevent further esophageal dilation. This is attempted via pharmacologic, endoscopic, or surgical means. The choice depends on the patient's comorbidities and therefore their candidacy for operative intervention.

In addition to reviewing the pathogenesis and diagnostic workup of achalasia, the various treatment modalities and newest emerging therapies that are hoped to evolve the field and improve treatment efficacy will be discussed in depth.

Esophageal structure and motor innervation

The esophagus consists of four primary layers – the mucosa, submucosa, muscularis propria, and adventitia.⁷ The muscularis propria consists of both a circular and longitudinal muscle layer. It gradually transitions from predominantly striated, skeletal muscle in the upper esophagus to predominantly smooth muscle in the lower esophagus. The esophagus terminates around the area of the diaphragmatic hiatus where

Figure 1 (Continued)

Figure 1 (Continued)

Figure 1 (A–D) Diagnostic tests for achalasia.

Notes: (A) Barium esophagram; (B) endoscopic appearance of achalasia; (C) chest computed tomography showing sigmoid esophagus; and (D) esophageal manometry showing type II achalasia.

there exists a 2–4 cm circular muscle layer, termed the lower esophageal sphincter.⁷

Esophageal motor innervation occurs through the vagus nerve via the intrinsic enteric nervous system; namely, the myenteric or Auerbach's plexus. The origin of neural innervation for the striated muscle of the proximal esophagus differs from that of the smooth muscle of the distal esophagus. The striated muscle of the proximal esophagus is predominantly innervated by somatic efferent fibers that have cell bodies originating from the nucleus ambiguus. They terminate on the motor end plate via cholinergic receptors.^{8,9} Alternatively, the smooth muscle of the distal esophagus is innervated by preganglionic neurons with cell bodies originating in the dorsal motor nucleus and terminating on the fibers of the myenteric plexus.^{10,11} The esophageal musculature (including the LES) is then innervated by postganglionic fibers. These consist of both excitatory neurons, which release acetylcholine resulting in esophageal and LES contraction, and inhibitory neurons, which release nitric oxide and vasoactive intestinal peptide resulting in relaxation.^{12,13} These neurons work together in a coordinated manner once a food or liquid bolus enters the esophagus to result in peristalsis that moves the bolus from the esophagus into the stomach.

In a normal functioning esophagus, inhibitory neurons are activated first to release nitric oxide, which relaxes the esophagus and allows for accommodation of the incoming food bolus. Following bolus front esophageal relaxation, there is a sequential activation of the excitatory neurons proximal to the bolus front to release acetylcholine, which then propels the food bolus forward.

Eventually, the peristaltic waves will propel the food bolus across the esophagogastric junction (EGJ) into the stomach. EGJ is a high-pressure area that is comprised of the LES, crural diaphragm, and proximal gastric cardia.⁷ Normal resting lower esophageal pressure is 10–30 mmHg, which functions to prevent reflux of gastric contents back into the esophagus. When the food bolus reaches the LES, it relaxes to allow passage into the stomach. This is achieved via activation of the inhibitory neurons resulting in the release of nitric oxide.

Pathogenesis of achalasia

The primary pathophysiologic disturbance resulting in achalasia is the selective loss of inhibitory innervation from the myenteric plexus of the distal esophagus and LES.¹⁴ The etiology for this process is unknown; however, genetics,

infection, and autoimmune contributors have been discussed. The process may be an autoimmune phenomenon initiated by an indolent viral infection in a genetically predisposed host.¹⁵ Ultrastructural studies of esophageal tissue have found inflammatory infiltrate in the myenteric plexus of patients with achalasia compared to no inflammatory infiltrate in patients without achalasia.^{2,16} Additionally, a few case-control studies have suggested an association with HLA class II antigens and the development of idiopathic achalasia.^{17,18} Furthermore, Ruiz-de-Leon et al¹⁹ revealed that achalasia patients with these associated class II HLA antigens had a higher prevalence of circulating antimyenteric autoantibodies. This is strongly suggestive of an autoimmune component as the etiology. However, one should note that not all patients with achalasia have these associated HLA antigens.²⁰

The consequence of the myenteric plexus inflammation is the degeneration of inhibitory postganglionic neurons of the esophagus and LES.^{21,22} This results in unopposed cholinergic stimulation leading to impaired relaxation of the LES and hypercontractility of the distal esophagus.⁷

Diagnosis of achalasia

The diagnosis of achalasia is typically suspected in a patient with dysphagia to both solids and liquids with associated regurgitation of undigested food. Complimentary tests include esophagogastroduodenoscopy and barium esophagram; however, definitive diagnosis should only be made following evaluation of esophageal motor function with manometric testing.¹ The following are the diagnostic modalities often employed in achalasia.

Esophageal manometry

Esophageal manometry is the gold standard for the diagnosis of achalasia. It functions to assess esophageal pressures along the length of a flexible catheter inserted into the esophagus. The classic manometric finding of aperistalsis of the esophageal body and incomplete LES relaxation without evidence of mechanical obstruction is strongly supportive toward the diagnosis of achalasia.²³ Other findings that include increased resting LES pressure and simultaneous nonpropagating contractions are also suggestive of the diagnosis, however, these are not required.²⁴

Manometry, as a diagnostic tool, has evolved significantly over the past decade from conventional catheters with pressure sensors spaced 3–5 cm apart utilizing solid-state technology or a water-perfused extrusion catheter to high resolution manometry where pressure sensors are placed 1 cm apart with either water-perfused extrusion or solid-state technologies.¹

High resolution manometry can display pressure data as esophageal topography plots (Figure 1D). Esophageal pressure topography gives the clinician the advantage of differentiating achalasia into three distinct subtypes that have important therapeutic outcome implications.²³ Subtype II has the most favorable prognosis, whereas subtype III is the most difficult to treat. The prognosis of subtype I is somewhere in between.^{23,25,26}

Barium esophagram

Esophageal dilation with a gradual taper down to the gastroesophageal junction giving a “bird’s beak” appearance is the classic description of achalasia on barium esophagram (Figure 1A). Additional findings include aperistalsis and poor emptying of barium.¹ Signs suggestive of late- or end-stage achalasia include tortuosity, angulation, and megaesophagus.¹

An additional role for contrast radiography is the assessment of esophageal emptying following treatment of achalasia. Symptom relief often does not parallel esophageal emptying. Therefore, objective assessment of treatment response can be helpful in identifying patients at risk of failed treatment. This is accomplished by timed barium esophagram where the barium column height is measured at 1 and 5 minutes after upright ingestion of a large barium bolus.²⁷ Subsequent studies have revealed the usefulness of timed barium esophagram for identifying patients at risk of failed treatment.^{28,29} Computed tomography can also be used to support an underlying diagnosis of achalasia and show the extent of disease, especially in those with sigmoid esophagus (Figure 1C); however, it is less sensitive and not commonly employed.

Endoscopy

Most patients presenting with dysphagia require esophagogastroduodenoscopy primarily to rule out a mechanical obstruction due to cancer that can mimic achalasia both clinically and manometrically. This is termed “pseudoachalasia.”^{30–32} Similar to achalasia, mechanical obstruction can manometrically result in impaired LES relaxation and aperistalsis or spastic contractions of the esophageal body.³³

Endoscopic findings of achalasia range from a grossly normal appearance to a tortuous, dilated sigmoid esophagus with retained food and saliva (Figure 1B).¹ Oftentimes, the gastroesophageal junction will have a puckered appearance. Intubation of the stomach may give mild resistance; however, a strong resistance should raise suspicion of pseudoachalasia.¹

Of note, patients with achalasia can develop candidiasis secondary to esophageal stasis. Endoscopic evidence of candidiasis in the setting of immunocompetence suggests an esophageal motility disorder.⁷

Clinical management of achalasia

At the moment, there are no therapies that will reverse the loss of the inhibitory interneurons of the myenteric plexus and restore normal esophageal motility. Current treatment options aim to reduce the hypertonicity of the LES to improve esophageal emptying by gravity. This is attempted via oral pharmacologic therapy, endoscopic therapy, or surgery. The choice of treatment is dependent on patient age, comorbidities, severity, patient preference, and locally available expertise.³⁴ Currently, pneumatic dilation (PD) and surgical myotomy are considered the most effective therapies. Other options are employed in those who are not candidates for these more effective therapies.¹ Regardless of the intervention, LES hypertonicity returns over time requiring repeat intervention. The decision on treatment options is based on several factors, including operative candidacy and durability (Table 1).

Oral pharmacologic therapy

Oral pharmacologic therapies are considered the least effective treatment option for achalasia.³⁵ The clinical response to these agents is short lived and their side effect profile is

unfavorable. Additionally, they do not provide complete alleviation of symptoms and therefore they are usually reserved for patients who are poor candidates for more effective therapies (PD, surgical myotomy) or in those who have failed botulinum toxin injections (BTIs).¹ The aim of these medications is to induce smooth muscle relaxation of the LES thereby facilitating passage of esophageal contents into the stomach. The two most commonly employed medications are calcium channel blockers and long-acting nitrates. Sildenafil, a phosphodiesterase-5-inhibitor, is another option.³⁶ Other less commonly used medications include anticholinergics, β -adrenergic agonists, and theophylline.

Endoscopic pharmacologic therapy

Botulinum toxin, a potent inhibitor of acetylcholine release from the presynaptic terminals by cleaving the SNAP-25 protein, is a useful treatment strategy for patients who are unable to tolerate more invasive therapies, such as PD or surgical myotomy. The objective of this therapy is to block unopposed cholinergic stimulation caused by the selective loss of inhibitory interneurons that release neurotransmitters to relax the LES.³⁷

The technique involves injecting up to 100 units of toxin with a sclero-needle just proximal to the squamo-columnar junction evenly distributed over four quadrants. Doses greater than 100 units are shown to be no more effective.³⁸ Complications related to the procedure are rare and typically involve chest pain seen in 16%–25%. Rare, more serious, complications include mediastinitis and an allergic reaction to an egg-based protein. Additionally, repeated BTIs can lead to subsequent submucosal fibrosis making future surgical myotomy difficult.^{39–41} Therefore, BTI should be reserved for patients in whom PD and surgical myotomy are precluded due to operative risk factors.⁴²

The response rate in the first month of treatment is high at 80%–90%; however, the therapeutic effect wanes rapidly over time such that ~50% of patients are symptomatic at 1 year.^{38,43,44} Thus, repeat treatments every 6–12 months are often required. Factors predictive of a favorable and prolonged response to BTI are older age (>40 years old), a type II manometric pattern, and a decreased basal LES pressure following treatment.⁴⁴

Pneumatic dilation

PD, a procedure employing air pressures to disrupt or fracture the LES circular muscle fibers, is the most effective nonsurgical option in the treatment of achalasia.^{1,5} Currently, the most widely used balloon dilator is the Rigiflex, a nonradiopaque

Table 1 Pros and cons of conventional treatments for achalasia

Therapy	Pros	Cons
Medical therapy	<ul style="list-style-type: none"> • On demand • Minimal risk • Option for nonoperative candidates 	<ul style="list-style-type: none"> • Least effective treatment option³⁵ • Not durable
Botulinum toxin injection	<ul style="list-style-type: none"> • Good option for nonoperative candidates • Short procedure time 	<ul style="list-style-type: none"> • Durability of 6–12 months⁴⁴
Pneumatic dilation	<ul style="list-style-type: none"> • Most effective nonsurgical option^{1,5} • Durability 2–5 years⁹⁶ • Procedure time <30 minutes • Short recovery time 	<ul style="list-style-type: none"> • Perforation (1%–5%)
Surgical myotomy	<ul style="list-style-type: none"> • Durability 5–7 years⁹⁶ • Procedure time ~90 minutes 	<ul style="list-style-type: none"> • General anesthesia required • Hospital stay of 1–2 days
Esophagectomy	<ul style="list-style-type: none"> • For end-stage disease • Treatment-resistant achalasia 	<ul style="list-style-type: none"> • High morbidity and mortality • Anastomotic strictures • Chronic vomiting in some

graded size polyethylene balloon. Another less commonly employed and essentially abandoned balloon dilator is the Witzel dilator that comes in only one size (4.0 cm balloon). This has fallen out of favor over the past years.

With Rigidflex dilators, the procedure can be performed under radiologic guidance (fluoroscopy); although balloon positioning under direct endoscopic guidance can also be employed.^{45,46} The dilators are available in three diameters (3.0, 3.5, and 4.0 cm). There are two different strategies for performing PD that include a single dilation approach and a graded dilation approach. When employing the graded approach, relief of symptoms is possible in 50%–93% of patients.^{5,35,47,48} One cross-sectional study demonstrated that symptomatic response to a single PD was 62% at 6 months and 28% at 2 years compared to 90% at 6 months and 44% at 6 years in the graded PD cohort.⁴⁷

Graded PD is performed by an initial dilation at 3.0 cm, then 3.5 cm, and finishing at 4.0 cm with 4–6 weeks in between dilations. Reassessment of symptoms and LES pressure can be performed between each session to determine the necessity of subsequent treatments. Additionally, the rate of perforation may be lower with the graded dilation approach.¹

It is estimated that a third of patients treated with PD will experience symptom relapse within 4–6 years.¹ Predictive factors of a poor clinical response to treatment include age <40 years,^{49–51} male sex,⁵² LES pressure after dilation greater than 10–15 mmHg,⁵³ and continued symptoms after one or two treatments.^{52–55} Additionally, males younger than 45 years of age may not be as responsive to the serial approach. This is possibly due to thicker LES musculature. In these patients, it is recommended to either start with PD at 3.5 cm or proceed straight to surgical myotomy as the initial step in management.¹ Of note, patients with a type II high resolution manometry pattern have been shown to have better outcomes.²⁵

All patients being considered for PD must also be appropriate surgical candidates as esophageal perforation is a known complication of this procedure. The rate of perforation is ~1.9% but is shown to range from 0% to 5%.^{47,56} Although there are no factors predictive of perforation, it is believed to most commonly occur during the initial dilation and is thought to be related to improper balloon positioning.⁵⁷ Small, asymptomatic perforations can be managed conservatively with parenteral nutrition, antibiotics, and stent placement.⁵⁸ However, for large perforations with mediastinal contamination, surgical repair through thoracostomy is required.¹ An additional complication includes gastroesophageal reflux disease (GERD), which is seen in 15%–35% of

patients following PD. Therefore, starting a proton pump inhibitor following PD in those with preexisting GERD is recommended.⁵⁹

Surgical myotomy

Surgical myotomy, a technique involving the division of the circular muscle fibers of the LES, was initially performed via an open thoracotomy and laparotomy approach. Studies at the time revealed good response with 60%–94% of patients achieving symptomatic improvement when followed over 1–36 years.³⁵ However, over time, this approach was replaced with more minimally invasive techniques; first with thoracoscopy which was then replaced with laparoscopic myotomy because of improved morbidity and faster recovery time.⁶⁰ Additionally, these minimally invasive techniques can be performed with similar efficacy to the open approach; 94% versus 84%, respectively.³⁵

There are no randomized control trials comparing the different approaches of surgical myotomy. All published data in this area are prospective or retrospective cohort and case–control studies. A systematic review analyzing surgical techniques in 4,871 patients reported patient symptom improvement after all surgical myotomies. This included 84.5% of those who underwent the open transabdominal approach, 83.3% of those with the open transthoracic approach, 77.6% of those with the thoracoscopic approach, and 89.3% of those who had a laparoscopic myotomy.⁴⁸ A subset of the analysis comparing studies with laparoscopic Heller myotomy (LHM) (3,086) and the thoracoscopic approach (211) showed better symptomatic improvement with the laparoscopic approach compared to the thoracoscopic approach (89.3% vs 77.6%, $P=0.048$).⁴⁸

GERD is a known and frequent complication following surgical myotomy thereby making intraoperative fundoplication a consideration to remedy it. The incidence of postoperative reflux symptoms is reported to be lower for the laparoscopic than for the thoracoscopic approach (28.3% vs 14.9%, $P=0.03$) and open transthoracic approach (24.6% vs 14.9%, $P=0.04$).⁴⁸ Reflux may be less if fundoplication is added to myotomy (41.5% without fundoplication vs 14.5% with fundoplication, $P=0.001$).⁴⁸ A randomized controlled trial comparing myotomy with or without fundoplication reported that performing intraoperative fundoplication was associated with a lower incidence of postoperative reflux.⁶¹ Therefore, in the guidelines published by the Society of American Gastrointestinal and Endoscopic Surgeons, it is recommended to perform fundoplication in patients who undergo myotomy.⁶² Additionally, the rate of postoperative

dysphagia is shown to be independent of whether or not a fundoplication was performed after myotomy.⁴⁸ Of note, Rawlings et al⁶³ demonstrated in a randomized control trial comparing anterior Dor with posterior Toupet fundoplications that both provide similar outcomes in terms of postoperative reflux following LHM.

Of note, robotic surgery is an emerging minimally invasive alternative to LHM. It is a computer-assisted device under the remote control of a surgeon. It has the benefit of providing a magnified surgical field that allows for more precise movements thereby reducing complications.⁶⁴

Esophagectomy

“End-stage” achalasia, characterized by a dilated and tortuous esophagus (megaesophagus or sigmoid esophagus), is often unresponsive to conventional treatments for achalasia. Although PD is ineffective, surgical myotomy should still be considered the initial treatment before consideration of the more morbid esophagectomy. Two recent studies involving patients with megaesophagus revealed that surgical myotomy resulted in improvement of symptoms ranging from 72% to 92%.^{65,66} When symptoms are unresponsive to myotomy, esophagectomy should be the next step for consideration.⁶⁷ Observational studies do show symptomatic response of up to 80% with esophagectomy; however, its association with a greater morbidity and mortality make it a last resort treatment modality.⁶⁸

Advances in treatment for achalasia

Peroral endoscopic myotomy

Peroral endoscopic myotomy (POEM), a minimally invasive endoscopic technique, is one of the most recent advances in the treatment of achalasia (Table 2). It was first described in a case series published in 1980 by Ortega et al⁶⁹ where two

1 cm long myotomies were performed through the mucosa at a depth of 3 mm. However, this was not further studied until 2007 when Pasricha et al⁷⁰ demonstrated endoscopic myotomy in a porcine model. Then, in 2010, Inoue et al⁷¹ published a prospective trial of 17 patients undergoing endoscopic myotomy that revealed significant reduction in the index of dysphagia symptoms (10 to 1.3, $P=0.0003$) as well as resting LES pressure (52.4 to 19.9 mmHg, $P=0.0001$). No serious complications were reported. It was at this point where endoscopic myotomy became adopted into clinical practice.⁷² In 2012, von Renteln et al⁷³ published another prospective trial. It included 16 patients and illustrated symptomatic response in 94% after 3 months. Furthermore, resting LES pressure was reduced from 27.3 to 11.8 mmHg ($P<0.001$). In 2014, Bhayani et al⁷⁴ conducted a prospective observational study that compared 64 patients treated by LHM and 37 by POEM. It showed that mean operative time and length of stay were significantly higher in the LHM cohort but complication rates were similar. Patient symptoms, manometry, and postoperative esophageal acid exposure revealed similar outcomes among the two groups.

The preparation for POEM begins with a liquid diet 1–5 days prior to the procedure to minimize residual food in the esophagus.⁷⁵ The first step in the procedure involves injection of 10 mL of saline solution with contrast (methylene blue or indigo carmine) to the central esophagus 10–16 cm proximal to the squamo-columnar junction.⁷² The purpose of this is to expand the submucosa so it is easily accessed for dissection and tunnel formation. This allows safer access to the circular muscle layer. Following this, a 2 cm incision is made to gain access into the submucosal space. Then, a submucosal tunnel is dissected through the EGJ and 2–3 cm into the gastric cardia.⁷⁶ Once access is made to the circular muscle layer of

Table 2 Studies evaluating the efficacy of peroral endoscopic myotomy (POEM)

Author	Year	Study design	Inclusion criteria	Population	Outcome
Inoue et al ⁷¹	2010	Prospective observational	Adults >18 years old Proven achalasia by manometry	17 patients treated by POEM	<ul style="list-style-type: none"> • Significant reduction in the index of dysphagia symptoms • Significant reduction in resting LES pressure
von Renteln et al ⁷³	2012	Prospective observational	Adults >18 years old Symptomatic achalasia Medical indication for LHM or PD	16 patients treated by POEM	<ul style="list-style-type: none"> • Postprocedure Eckardt symptom score ≤ 3 in 94% • Significant reduction in resting LES pressure
Bhayani et al ⁷⁴	2014	Prospective observational LHM vs POEM	Patients with achalasia LHM or POEM from 2007 to 2012 at a single institution	101 patients LHM (n=64; 42% Toupet and 58% Dor funduplications) or POEM (n=37)	<ul style="list-style-type: none"> • 1-Month Eckardt scores significantly better for POEMs • 6-Month Eckardt scores similar improvements (1.7 vs 1.2, $P=0.1$) • Mean hospitalization significantly higher for LHMs

Abbreviations: LES, lower esophageal sphincter; PD, pneumatic dilation; LHM, laparoscopic Heller myotomy.

the LES, the myotomy is usually extended to 6 cm into the esophagus and 2 cm below the EGJ.²⁰

Serious adverse events are rare with POEM. They occur at a rate of <0.1% with the most common serious event being perforation.⁷⁷ Another, albeit less serious, complication following POEM is GERD. In carefully selected patients, some studies have shown short-term postoperative clinical symptoms of GERD following POEM is 10.9%, comparable to that of LHM.⁷⁸

Self-expanding metal stents

The use of esophageal self-expanding metal stent (SEMS) has long been beneficial in the treatment of esophageal malignancies, esophageal perforations, and anastomotic leaks. There have been a few studies published in the recent past that have described the utility of SEMS in benign esophageal disease, particularly achalasia (Table 3).^{79,80}

In 2009, Zhao et al⁸¹ published a prospective observational study that concluded temporary SEMS to be a safe and effective modality in the management of achalasia with very good long-term symptomatic response rates. It involved 75 patients with achalasia who were treated with a temporary 30 mm diameter SEMS. They were placed under fluoroscopic guidance and removed via gastroscopy 4–5 days later. Follow-up was arranged at 6 months, 1 year, 3–5 years, 5–8 years, 8–10 years, and >10 years. Clinical response was 100% at 1 month and 83.3% at follow-up past 10 years. Complications were few but included migration (5.3%), chest pain (38.7%), and reflux (20%). There were no perforations or 30-day mortality.

Cheng et al,⁷⁹ in 2010, published another prospective observational study comparing the efficacy of 20, 25, and

30 mm diameter temporary SEMS. It involved a total of 90 patients with follow-up arranged at 6 months and 1, 3–5, 5–8, 8–10, and >10 years. The study found that patients who received the 30 mm diameter SEMS had the best clinical response and lowest incidence of stent migration. It found that the clinical symptomatic remission rate with 30 mm SEMS at >10 years was 83.3%. This is comparable to the long-term clinical response of those who underwent LHM. In 2010, Li et al,⁸² along with the same authors above at the same institution, published a prospective study comparing 30 mm SEMS with PD. It found that the clinical remission rate in those treated with PD was 0% at 10 years compared with 83.3% at 10 years in those treated with a 30 mm SEMS.

Although the results of the earlier studies are promising, they were published at a single institution and therefore their generalizability is questionable. Further investigation with randomized controlled trials will still be needed before they become accepted into clinical practice.

Endoscopic sclerotherapy

Two recent studies have been published describing the use of a sclerosing agent, ethanolamine oleate, in the treatment of achalasia (Table 4).^{83,84} The theory prompting its investigation was based on its necrotizing effect on the applied muscle.

In 2013, Moreto et al⁸³ published a study involving 103 patients who received endoscopic sclerotherapy every 2 weeks until dysphagia resolved. It reported a symptom remission rate of 90% at 50-month follow-up. In 2014, Niknam et al⁸⁴ performed a study involving 31 patients who received three treatments of ethanolamine oleate injections

Table 3 Studies evaluating the efficacy of self-expanding metal stent (SEMS)

Author	Year	Study design	Inclusion criteria	Population	Outcome
Zhao et al ⁸¹	2009	Prospective observational	Documented primary achalasia Recurrent dysphagia following pneumatic balloon dilation Life expectancy >6 months	75 patients who had a 30 mm SEMS placed	<ul style="list-style-type: none"> Symptom remission rate was 100% at 1 month and 83.3% at >10 years Significant reduction in 6-month mean dysphagia score
Cheng et al ⁷⁹	2010	Prospective observational	Documented primary achalasia Recurrent dysphagia following pneumatic balloon dilation Life expectancy >6 months	90 patients treated with 20 mm (n=30), 25 mm (n=30), or 30 mm (n=30) SEMS	<ul style="list-style-type: none"> 30 mm diameter SEMS group had the best clinical response and lowest incidence of stent migration Clinical symptomatic remission rate with 30 mm SEMS at >10 years was 83.3%, comparable to the long-term clinical response of those who underwent LHM
Li et al ⁸²	2010	Prospective observational trial comparing 30 mm SEMS with PD	Documented primary achalasia Recurrent dysphagia following pneumatic balloon dilation Life expectancy >6 months	155 patients allocated to PD (n=80) or 30 mm diameter SEMS (n=75)	<ul style="list-style-type: none"> Clinical remission rate in those treated with PD was 0% at 10 years compared with 83.3% at 10 years in those treated with a 30 mm SEMS

Abbreviations: PD, pneumatic dilation; LHM, laparoscopic Heller myotomy.

Table 4 Studies evaluating the efficacy of endoscopic sclerotherapy

Author	Year	Study design	Inclusion criteria	Population	Outcome
Moreto et al ⁸³	2013	Prospective observational	Diagnosis of achalasia by manometry	103 patients treated with ethanolamine oleate (EO) or polidocanol	<ul style="list-style-type: none"> Symptom remission rate of 90% at 50 months with EO, but only 65% with polidocanol
Niknam et al ⁸⁴	2014	Prospective observational	Poor candidates for PD; resistance to PD; high operative risk or unwillingness to undergo surgery; poor or no response to HM	31 patients who received three treatments of EO injections at 2-week intervals	<ul style="list-style-type: none"> Mean achalasia symptom score and mean volume of retained barium in TBE at 12 months were significantly reduced compared with preinjection scores

Abbreviations: PD, pneumatic dilation; TBE, timed barium esophagram; HM, Heller myotomy; EO, ethanolamine oleate.

at 2-week intervals. They found that the mean symptom score at 12 months was significantly reduced compared with preinjection scores. It is important to note that, if the use of this procedure is entertained, it should be considered only in those with refractory achalasia who are not candidates for PD or surgical myotomy because there is a thought that the LES fibrosis that ensues might make invasive therapies more difficult.⁸⁵

Comparison of therapeutic modalities

PD versus BTI

Multiple randomized controlled trials have been conducted comparing the efficacy of PD and BTI. In 2006, Leyden et al⁸⁶ published a systematic review of seven randomized controlled trials totaling 178 patients. It found similar outcomes at a short-term follow-up of 4 weeks from the initial procedure. However, three studies within the review recorded a 12-month follow-up that discovered a significant difference in response. It found 55 of 75 (73.3%) PD subjects were in symptomatic remission compared to 27 of 72 (37.5%) BTI subjects (relative risk 1.88, $P=0.0002$). Similar results were elucidated by a systematic review published by Wang et al⁸⁷ in 2009. Therefore, current evidence supports that PD is more effective than BTI in achieving long-term symptomatic response.

PD versus BTI-PD

In 2006, Mikaeli et al⁸⁸ performed a randomized controlled trial comparing PD alone versus BTI before PD. At 1-year follow-up, it found remission rates were slightly higher in the BTI-PD group (77%) compared with the group that received PD alone (62%). In 2009, Zhu et al⁸⁹ published a randomized controlled trial that compared PD alone versus BTI alone versus PD with BTI 15 days later. All subjects were followed for 2 years. At 2 years, clinical remission was achieved in 13.7% treated with BTI alone, 35.7% in those

treated with PD alone, and 56.6% in those who received combination therapy. However, despite the earlier evidence, given the concern for fibrosis induced by BT, in clinical practice BT is not combined with pre- or post-PD in those who are candidates for definitive therapy with either PD alone or surgical myotomy.

PD versus LHM

In their systematic review, Campos et al⁴⁸ compared the efficacy of LHM and PD. It totaled 3,086 patients treated with LHM and 1,065 treated with PD. The study demonstrated significantly improved symptomatic relief in those treated with LHM compared to those treated with PD at 12 months (89.3% vs 68.2%) and past 36 months (89.3% vs 56.3%).

More recently, in 2011, Boeckxstaens⁹⁰ conducted a randomized controlled trial comparing LHM to PD. In all, 95 patients were randomized to receive PD and 106 patients were randomized to undergo LHM with a mean follow-up time of 43 months. The primary outcome was therapeutic success (as defined by a drop in Eckardt score to <3). It found a comparable success rate for both treatments at 1 year (90% in PD vs 93% in LHM) and at 2 years (86% in PD vs 90% in LHM).

A recent meta-analysis published by Weber et al⁹¹ in 2012 found that LHM has greater durability than PD. It included 36 studies with 3,211 patients in the PD group and 1,526 patients in the LHM group. In those treated with PD, it found the mean 5-year remission rate to be 61.9% and mean 10-year remission rate to be 47.9%. In those treated with LHM, it found the mean 5- and 10-year remission rates were 76.1% and 79.6%, respectively.⁹¹ It also found a perforation rate for those treated with LHM to be double that of those treated with PD (4.8% vs 2.4%; $P<0.05$).

Therefore, based on the available evidence, success rates for PD and LHM are believed to be comparable although LHM may be associated with greater long-term durability, especially in younger males.

Treatment algorithm

A generally agreed upon stepwise treatment algorithm for achalasia is illustrated in Figure 2. Many factors are considered in the selection of the appropriate therapy. They include age, sex, comorbidities and surgical risk, type of achalasia, and available expertise.⁹²

In general, patients with achalasia who are deemed good surgical candidates should be referred for consideration of PD or LHM. Although evidence has shown both therapies to be equally effective in the short term, LHM is the most durable form of treatment for long-term symptom remission, especially in younger male patients.^{1,91}

One recent study determined outcomes in the treatment of achalasia based on manometric subtype. For PD, it reported response rates of 96% in patients with type II achalasia, 56% for type I, and 29% for type III.⁹³ Therefore, PD seems to be most effective in the treatment of type II achalasia. Although PD is shown to induce long-term symptomatic remission, multiple sessions are often required due to symptom recurrence. PD is considered a failed treatment when there is lack of symptom improvement after 2–3 sessions or following the use of the largest diameter balloon. In these situations, referral to surgery for consideration of surgical myotomy is most appropriate.⁷² Furthermore, it is appropriate to consider PD in patients who have failed initial treatment with surgical myotomy and who have recurrence of symptoms.

Surgical myotomy is shown to be an effective therapy for inducing long-term symptomatic remission.⁹¹ In patients who are good operative candidates, it is recommended in adolescents and young adults (especially male),⁹⁴ patients with achalasia type III,⁹³ patients with pulmonary symptoms, and those who have not responded to two to three sessions of PD or following the use the largest diameter balloon.⁷²

Figure 2 Treatment algorithm for achalasia.

BTI is considered first-line therapy in patients with advanced age, short life expectancy, and significant comorbidities who are high risk of PD and surgical myotomy.⁴² Oral pharmacologic therapies with nitrates, calcium channel blockers, and phosphodiesterase-5-inhibitors (sildenafil) are generally recommended for patients who cannot undergo more definitive treatment with PD/LHM or in whom BTI has failed. They theoretically function to reduce pressure at the LES but the efficacy is very poor. In general, BTI and oral pharmacologic therapies should only be considered in high-risk patients or as a stepping stone to more definitive therapies.⁹⁵

POEM is an emerging therapy for patients with achalasia but at this time there is no general consensus as to where it will fall within the achalasia treatment algorithm. Randomized controlled trials will have to be undertaken before it becomes widely accepted into clinical practice. However, the preliminary reports are promising for its role as a potential initial therapy in select group of patients.

Disclosure

The authors report no conflicts of interest in this work.

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