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Advances in the Treatment of Achalasia

*Jeffrey A. Blatnik, MD**
Jeffrey L. Ponsky, MD

Address
*Department of Surgery, University Hospitals Case Medical Center,
11100 Euclid 5047, Cleveland, OH 44106, USA
Email: Jeffrey.Blatnik@UHhospitals.org
Email: Jeffrey.Ponsky@UHhospitals.org

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Opinion statement

Achalasia, although rare, remains one of the most commonly diagnosed disorders of esophageal motility. It results from an idiopathic loss of ganglion cells responsible for esophageal motility and relaxation of the lower esophageal sphincter (LES). As a result, patients present with worsening dysphagia to both liquids and solids and often suffer from significant regurgitation of retained food in the esophagus. When the diagnosis of achalasia is suspected, patients should undergo evaluation with esophageal motility testing, endoscopic examination, and contrast esophagram. Once the diagnosis of achalasia has been established, options for treatment rely on controlling patient symptoms. Medical options are available, but their effectiveness is inconsistent. Endoscopic options include injection of botulinum toxin, which can achieve good short-term results, and pneumatic balloon dilation (PBD), considered the most effective non-surgical option. Surgical options, including laparoscopic, open, or endoscopic myotomy, and provide long-lasting results. This chapter will review achalasia and the treatment options available.

Introduction

Achalasia is a disorder of esophageal motility that is characterized by a failure of relaxation of the LES and, frequently, aperistalsis of the esophagus. Although relatively rare, with an annual incidence of 1 in 100,000 individuals, it is still one of the most commonly diagnosed disorders of esophageal motility [1]. Achalasia affects both men and women equally, with a peak onset between the ages of 25 and 60 years.

The most common complaint of patients presenting with achalasia is dysphagia to both liquids and solids (94 %). As symptoms progress, patients often experience regurgitation of undigested food (76 %).

Less common symptoms include heartburn (52 %), chest pain (41 %), and weight loss (35 %) [2]. The onset of achalasia is often insidious, with gradual progression of symptoms over time. Patients will often suffer for years prior to seeking medical care, and then are frequently misdiagnosed with gastroesophageal reflux disease (GERD) [3]. Achalasia should be considered in the differential for all patients with a longstanding history of dysphagia who fail to improve with medical management of GERD. The diagnosis of malignancy must be ruled out in all patients who present with a rapid onset of symptoms and associated weight loss.

Achalasia results from a loss of the neurons within the esophageal wall. The neurons (or ganglion cells) reside within the myenteric plexuses, and in achalasia patients, they are subject to inflammatory degradation [4]. The inhibitory neurons that affect the relaxation of the LES tend to degenerate preferentially, and as a result, the LES fails to relax with swallowing. The exact cause for the loss of neurons is not completely understood.

Diagnosis of achalasia

The diagnosis of achalasia should be sought in patients who present with progressive symptoms of dysphagia and regurgitation that do not improve with therapy for GERD. The hallmark of diagnosis of achalasia is failure of the LES to relax and aperistalsis of the esophagus, and the use of esophageal manometry is necessary to confirm the diagnosis [5]. Manometry may occasionally reveal an increased basal LES pressure or normal- to high-amplitude simultaneous esophageal contractions [6].

Options for esophageal manometry can be divided into conventional manometry and high-resolution manometry. In conventional manometry, the pressure sensors are spaced more widely apart (3–5 cm) and are able to demonstrate the presence of aperistalsis in the distal esophagus and incomplete LES relaxation, which is what differentiates achalasia from other disorders associated with aperistalsis.

The advent of high-resolution manometry, which includes pressure sensors at a much smaller interval, allows for more detailed manometric results than conventional manometry. Using techniques to interpolate the data between the pressure sensors allows dynamic-pressure topography [7]. The more widespread use of dynamic-pressure topography has facilitated the classification of achalasia into further subtypes based on the pattern of esophageal pressure.

- Type I (classic) – absent peristalsis with swallowing
- Type II – simultaneous contractions of the esophagus with amplitudes <40 mm Hg
- Type III (spastic) – preserved contractions of the esophagus, but with abnormally high pressure.

The ability to subtype patients into different categories has implications on treatment selection [8, 9]. It has been shown that type II achalasia may have the best prognosis following either pneumatic dilation or surgical myotomy. The success rate for type I patients is slightly less than type II, and type III patients have the worst prognosis.

In addition to the use of manometry, other imaging techniques can provide additional diagnostic utility. Plain chest radiograph may reveal a widening of the mediastinum due to a dilated esophagus. Barium esophagram is more useful and can demonstrate a dilated esophagus, the classic narrowing of the esophagogastric junction often referred to as a "bird-beak," and aperistalsis. Contrast esophagram can also reveal late-stage changes, including angulation and megaesophagus, which may impact treatment options. Finally, objective information on the ability of the esophagus to empty barium can be very helpful in comparing patients' pre- and postoperative status. In a procedure known as a timed-barium esophagram, the height of the barium column is measured at 1 and 5 minutes after ingestion. When performed after repair, this information can be useful in determining who may ultimately fail treatment [10].

Upper endoscopy is recommended in all patients who are undergoing evaluation for achalasia in order to exclude other causes, such as pseudoachalasia, which can mimic achalasia on esophagram and manometry [11]. Esophageal malignancy must be ruled out in older patients with a more rapid onset of dysphagia symptoms and associated weight loss [12]. In addition to evaluating for malignancy, endoscopic evaluation may reveal a dilated esophagus, retained food, and a narrow gastroesophageal junction, all consistent with achalasia. In patients with longstanding symptoms, one may occasionally find evidence of inflammatory changes or ulceration secondary to stasis.

More recently, the use of compliance testing has been selectively used in evaluating patients with achalasia. This is performed by using a functional luminal imaging probe (FLIP), which allows for dynamic imaging of the esophagogastric junction distention as a cylinder. The probe consists of an infinitely compliant bag that is filled with saline to assume the esophageal volume. Then, using electrodes placed 4 mm apart, the impedance and pressure in the system is analyzed to calculate the compliance of the esophagus and GE junction. Studies evaluating FLIP in patients with achalasia have shown impaired distensibility, and post-treatment assessment is associated with improved esophageal emptying and clinical response [13•].

Treatment of achalasia

Achalasia is a chronic disease process, and treatment options do not cure the patient of the disease but rather serve to alleviate the symptoms of dysphagia. Therapy focuses on reducing the elevated LES tone but does not address the aperistalsis. Therapeutic approaches should be tailored to the individual patient.

Pharmacologic therapy

Pharmacologic therapies aimed at reducing lower esophageal pressure are the least invasive option, but they are also the least effective. The main classes of oral medications include calcium channel blockers and long-acting nitrates, which function by temporarily causing smooth-muscle relaxation in the LES, allowing food to pass into the stomach. Studies

have shown that calcium channel blockers can decrease LES pressure by 13-49 %, although improvement in patient symptoms varies widely, from 0–75 % [14]. The calcium channel blocker most frequently used for achalasia is nifedipine. The peak effect occurs from 20 to 45 minutes after ingestion and can last anywhere from 30 to 120 minutes. Therefore, patients need to take the medication at least 30 minutes prior to their planned meal. In addition to calcium channel blockers, sublingual isosorbide dinitrate has been shown to have some efficacy in treating achalasia symptoms. The peak duration of activity is slightly shorter than calcium channel blockers, so this this can be taken 10–15 minutes before meals. Sublingual isosorbide dinitrate is effective at decreasing LES pressure by 30–65 % and providing symptom improvement in 5–87 % of patients. Proposed alternative medications include anticholinergics, theophylline, beta-adrenergic agonists, and phosphodiesterase-5-inhibitors such as sildenafil. The primary challenge with medical therapy for achalasia is the side effects, including headaches and hypotension, which are dose-limiting and often prevent patients from taking the medications for a prolonged period of time. The only study completed to date comparing nifedipine with sublingual isosorbide dinitrate demonstrated a slight, clinically insignificant advantage in reduction of LES pressure to nifedipine [15]. Pharmacologic therapy should be reserved for patients who are medically unfit or who are unwilling to undergo more definitive therapy such as pneumatic dilation or surgery.

Endoscopically delivered pharmacologic therapies

In addition to oral medications, botulinum toxin therapy is an option to reduce LES pressure. Long-term effects of botulinum toxin are inferior to pneumatic dilation or surgical myotomy and should therefore be reserved for patients who are not good surgical candidates. Injection of botulinum toxin is performed by passing an endoscope to the LES, and then injecting a total of 100 units of toxin directly into the LES. This achieves a reduction of lower esophageal pressure by 50 % and can result in improvement in symptoms in 75 % of patients after 1 month [16]. However, the effects of botulinum toxin eventually wear off, and upwards of 50 % of patients need additional treatment after 6–12 months [17]. Surprisingly, a small percentage of patients report long-term improvement in symptoms following botulinum toxin injection, even after the effect of the injection has worn off. In addition to short-term therapeutic effects, the injection into the LES can sometimes cause scarring, making surgical myotomy more challenging [18].

Pneumatic dilation

Pneumatic balloon dilation (PBD) can be a definitive treatment for achalasia for some patients. This method involves the use of serial pneumatic dilations and should be performed by an experienced endoscopist under either endoscopic or fluoroscopic guidance. The goal of pneumatic dilation for achalasia is to fracture rather than just stretch the LES musculature, and therefore standard balloon or bougie dilation are not sufficient. Although numerous protocols have been proposed, the current standard involves initial dilation with a 3.0 cm-diameter balloon, which can be increased to a

diameter of 3.5 or 4.0 cm. This approach is often performed in an incremental fashion and can be repeated if necessary. The treatment not only leads to improved symptom control in the long-term (44 % vs. 28 %), but also to lower risk for esophageal perforation [19]. Multiple studies have looked at pneumatic dilation and have shown it to provide symptom relief in 50–93 % of patients [19, 20]. These results are maintained over the short-term (12 to 24 months), but as time progresses, patients often have recurrence in symptoms (33 % at 5 years) [19, 21]. Following balloon dilation, all patients should undergo radiographic evaluation with a Gastrografin swallow to ensure that there was no esophageal injury [22].

Patients undergoing PBD must also be good surgical candidates, as the most serious complication following PBD is esophageal rupture, occurring in 2 % of patients [19, 23]. Identification of such a problem requires a high index of suspicion [24]. Small perforations may be considered for conservative therapy, including antibiotics, parenteral nutrition, and possible endoscopic stent placement, but large ruptures with mediastinal contamination should undergo prompt surgical repair. In addition to risk for esophageal rupture, patients who undergo PBD can often suffer from significant reflux symptoms (15–35 %), and these patients should be considered for proton pump inhibitor therapy. Finally, those patients who undergo PBD and eventually go on to require surgical myotomy may be at an increased risk for postoperative complications [25].

Surgical myotomy

The primary alternative to pneumatic dilation includes surgical myotomy of the LES, with or without fundoplication, which is currently often performed laparoscopically due to lower morbidity and faster recovery [26]. The technique involves cutting the LES muscle fibers beginning 6–8 cm proximal to the GE junction on the distal esophagus, and continuing it through the LES approximately 3 cm onto the body of the stomach. Some surgeons believe that patients are at increased risk of reflux symptoms following surgical myotomy, and thus include a fundoplication (typically 180° or Dor fundoplication). The addition of fundoplication has been shown to reduce the occurrence of reflux from 48 % to 9 %, without increasing dysphagia symptoms [27]. Initial symptom relief is reported in up to 90 % of patients, and prolonged relief is provided for up to 36 months [20]. Similarly to PBD, symptoms often return over time, with only 57 % of patients reporting lack of symptoms at 6 years [19]. In a large retrospective study evaluating 1,461 patients undergoing either pneumatic dilation (81 %) or surgical myotomy (19 %), the risk of requiring additional therapy after 1, 5, and 10 years was 37 %, 56 %, and 63 %, respectively, following pneumatic dilation and 16 %, 30 %, and 37 %, respectively, after myotomy [28]. In patients who fail surgical myotomy or have recurrence of symptoms, PBD still exists as a secondary approach.

Surgery is believed to be less cost-effective when compared with pneumatic dilation, as the upfront surgical costs and recovery period are greater, despite having similar long-term symptom relief. Complications associated with surgical myotomy include postoperative gastroesophageal reflux, perforation, pneumothorax, bleeding, and infection [24]. Although significant, if identified at the time of surgery, these complications can be dealt with immediately.

Pneumatic balloon dilation (PBD) versus surgical myotomy

Numerous studies have set out to evaluate PBD versus surgical myotomy for the treatment of achalasia. The most thorough study to date was from the Achalasia Trial Investigators [29••]. In this study, a total of 201 patients with newly diagnosed achalasia were randomly assigned to receive pneumatic dilation or laparoscopic Heller's myotomy (LHM) with Dor fundoplication, and the mean follow-up period was 43 months. There was no difference in rate of therapeutic success at 1 year (90 % for pneumatic dilation and 93 % for LHM) or 2 years (86 % for pneumatic dilation and 90 % for LHM). There were also no significant differences in secondary outcomes, including pressure at the LES, esophageal emptying, or quality of life. Perforation of the esophagus occurred in 4 % of patients undergoing pneumatic dilation, and mucosal tears occurred in 12 % during LHM. Based on this study, the authors concluded that after 2 years of follow-up, there was no difference in therapeutic success between patients undergoing pneumatic dilation or Heller's myotomy. The results of their study are similar to results seen in a smaller randomized study of 51 patients [30].

Taking into consideration the similar outcomes regarding resolution of symptoms, researchers have evaluated PBD versus LHM with regards to the cost effectiveness. The most recent study, which included 5- and 10-year estimates, predicted costs for PBD of $7,717 versus $11,804 for LHM [31]. These findings are similar to previous studies, all of which have shown PBD to be more cost-effective when compared with LHM [32, 33].

Esophagectomy

In patients who have exhausted all other therapeutic options and have progressed to end-stage achalasia, esophagectomy must be considered. These patients typically have signs and symptoms of megaesophagus, with significant dilation and tortuosity. As expected, esophagectomy carries a much greater morbidity and mortality than LHM or PBD, and should be reserved for patients who have failed all other options. Studies evaluating esophagectomy for achalasia are sparse. However, in retrospective series, improvement in symptoms has been reported in up to 80 % of patients, with mortality rates between 0–5.4 % [34].

Endoscopic myotomy

Recent advances in therapeutic endoscopy have led to the development of peroral endoscopic myotomy (POEM) for the treatment of achalasia. This technique involves creating a submucosal tunnel in the esophagus and using an endoscopic dissection knife to cut the circular fibers of the esophagus from about 10 cm proximal to the GE junction to 2 cm into the body of the stomach. The concept of a submucosal tunnel began with studies in natural orifice transluminal endoscopic surgery (NOTES) [35]. Initially developed in Japan, this technique has shown impressive early results, with resolution in symptoms in approximately 90 % of patients [36•].

Several short-term studies have been conducted comparing POEM with LHM and have shown similar results with regard to resolution of symptoms. Probably the most thorough study to date compared 101 patients over a 5-year period, evaluating patients at 1 and 6 months postoperatively [37••]. Patients demonstrated similar results for improvement in symptoms, operative time, and postoperative acid exposure in the esophagus, as well as reduced hospital length of stay. POEM was recently compared with LHM in a small series utilizing intraoperative FLIP to assess changes in the esophagogastric junction following intervention. In this small case series, both techniques resulted in similar improvement in esophagogastric junction distensibility [38]. Several other small studies published within the last year have shown similarly promising short-term results [39, 40]. Unfortunately, there have been no randomized trials to date comparing POEM with LHM or PBD, and data are scant regarding POEM's long-term success. As such, this technique is currently limited to select centers, although it is being adopted by more centers and may mature into a less invasive option for select patients in the future.

Treatment selection

A suggested treatment algorithm for patients with newly diagnosed achalasia is provided in Fig. 1. When selecting the ideal treatment for each patient, one must begin by taking into consideration the available expertise. Symptomatic patients who are appropriate surgical candidates should be advised of the risks and benefits of LHM and PBD, both of which have similar rates of symptom resolution. Ultimate selection of PBD or LHM should depend on the best outcomes and experience at the select institution. At this point, although POEM has shown impressive initial results, its use should be limited to select centers on a clinical trial protocol. Patients who are not believed to be candidates for surgical intervention should undergo either systemic pharmacologic therapy (either nifedipine or sublingual isosorbide dinitrate) or endoscopic pharmacologic therapy with botulinum toxin.

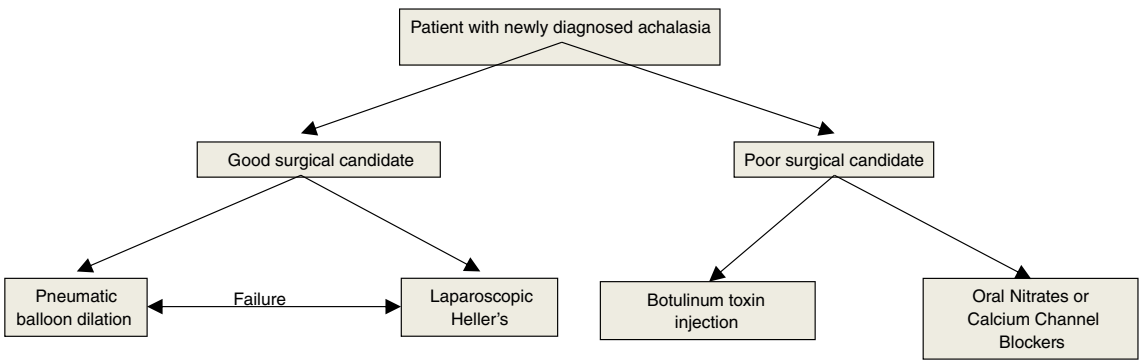

Figure 1. Recommended treatment scheme for newly diagnosed patients with achalasia.

Recurrent symptoms

Because therapy for achalasia is aimed at improving the symptoms rather than curing the underlying disease, many patients have recurrent symptoms after 2–3 years. Typically, patients who have undergone PBD as first-line therapy undergo repeat dilation for recurrent symptoms, often with continued symptom resolution [21]. However, those patients who fail repeated dilation may go on to require surgical intervention with myotomy. Patients who undergo LHM as first-line therapy and experience recurrent symptoms can also be managed with attempts at PBD, repeat myotomy, or botulinum toxin injection [41]. More invasive treatment such as esophagectomy is reserved for those patients who fail repeated attempts at myotomy or PBD.

Conclusion

Achalasia, a chronic disease with no cure, remains a challenge for clinicians. Current treatment options include pneumatic dilation or laparoscopic Heller's myotomy, which are aimed at alleviating the symptoms and show similar excellent results. Newer treatment options include POEM, where a surgical myotomy is performed endoscopically using a submucosal tunnel in the esophagus, with promising short-term results. The addition of new techniques for assessing the function and distensibility of the esophagogastric junction may help guide the selection of therapy based on a patient's severity of disease.

Compliance with Ethics Guidelines

Conflict of Interest

Jeffrey A. Blatnik has received royalties from UpToDate.

Jeffrey L. Ponsky has received honoraria from US Endoscopy.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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