Pneumatic dilation and botulinum toxin injection for achalasia

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INTRODUCTION

Achalasia is a motility disorder affecting the esophageal smooth muscle in which the lower esophageal sphincter (LES) fails to relax. It is thought to result from a selective loss of inhibitory nitrinergic neurons (which contain nitric oxide synthase) in the myenteric plexus, resulting in relatively unopposed excitation by the cholinergic system. Clinical symptoms may include dysphagia, chest pain, regurgitation, heartburn, and weight loss. The diagnosis is confirmed by esophageal manometry.

There is no cure for achalasia. Treatment is focused on palliating symptoms by decreasing LES pressure to facilitate the emptying of esophageal contents. This can be accomplished by mechanical disruption of the muscle fibers of the LES (for example, with pneumatic dilation or with endoscopic or surgical myotomy) or by biochemical reduction in LES pressure (for example, with injection of botulinum toxin).

This topic will discuss pneumatic dilation and botulinum toxin injection for the management of achalasia. The pathophysiology, clinical manifestations, diagnosis, and other treatment options for achalasia are discussed separately:

- (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis".)
- (See "Overview of the treatment of achalasia".)
- (See "Surgical myotomy for achalasia".)

- (See "Peroral endoscopic myotomy (POEM)".)

The recommendations that follow have been informed by guidelines from professional societies [1-3].

PNEUMATIC DILATION

The goal of pneumatic dilation (PD) is to weaken the lower esophageal sphincter (LES) by circumferentially stretching and, in some cases, tearing its muscle fibers [4].

Technique — There is no consensus on the optimal method for performing PD. Reported protocols have varied widely with regard to the types of dilators used, the maximum diameter of the balloon (2.4 to 5 cm), the pressure to which the balloon is inflated (100 to >1000 mmHg), the rate of balloon inflation (rapid versus gradual), the duration of balloon inflation (several seconds to five minutes), and the number of balloon inflations per dilating session (one to five) [5-7].

The balloon dilator commonly used in the United States is the Rigiflex balloon, which is passed over a guidewire and positioned via fluoroscopy across the LES. The balloon is available in three diameters (30, 35, and 40 mm). The smallest balloon is typically used for the first dilation (30 mm) [8]. If symptoms persist, the procedure can be repeated with incrementally larger balloons, and this has been referred to as the "graded approach."

We typically perform one balloon dilation per endoscopic session, with additional dilations being performed if symptoms persist or recur. (See 'Follow-up' below.)

Patients are advised to fast for at least 12 hours prior to the procedure. In addition, a liquid-only diet should be consumed for one or two days preceding the dilation in patients with clinical or radiographic evidence of severe food retention within the esophagus.

Prior to the procedure, the balloon is inflated and checked for leaks or deformities.

Prior to dilation, a diagnostic endoscopic examination is performed, with particular attention given to the cardia, where malignancy can mimic symptoms of achalasia (ie, pseudoachalasia). (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Differential diagnosis'.)

A guidewire is then passed through the biopsy channel of the endoscope into the stomach and the scope is withdrawn to the gastroesophageal junction. The distance between the incisors

and the gastroesophageal junction should be noted using the markings along the length of the scope.

The endoscope is then removed, taking care to maintain the position of the guidewire in the stomach. To aid with initial balloon placement, a marker (such as paper tape) can be placed on the shaft of the dilating catheter corresponding to the previously noted distance between the incisors and the gastroesophageal junction. This distance should be measured from the middle of the balloon on the dilating catheter so that, when inserted, the middle of the balloon will be positioned across the LES.

The balloon and catheter tip are lubricated and passed over the previously placed guidewire until the marker reaches the incisors. Using fluoroscopy, the balloon is then gradually inflated with air, noting the position of the developing "waist" in the balloon (image 1). Small adjustments usually have to be made in the position (deflating the balloon each time) to ensure that the waist occurs at the center of the balloon (this is critical for both efficacy and safety). We often inject a small volume of dilute contrast into the balloon to assist in radiographic visualization.

Procedural sedation administered by an anesthesia provider is often useful to ensure optimal sedation and airway management for this advanced procedure. (See "Anesthesia for gastrointestinal endoscopy in adults".)

Procedural sedation administered by the endoscopist is an alternative. When using this approach, we find it helpful to administer an additional dose of an intravenous opioid one to two minutes before the balloon is inflated because patients may experience pain during the dilation. (See "Gastrointestinal endoscopy in adults: Procedural sedation administered by endoscopists".)

After a satisfactory position is obtained, the balloon is fully inflated so that the waist is obliterated, taking note of the pressure within the balloon using an external gauge. In our experience, approximately 7 to 15 pounds per square inch (psi) of pressure is required for waist obliteration, which usually requires approximately 120 mL of air.

Inflation is maintained for 60 seconds, after which the balloon is rapidly deflated. We then perform a second full inflation for 60 seconds and again note the pressure required to obliterate the waist. This is usually at least 3 psi less than the initial pressure, thus indicating immediate improvement.

After the second inflation, the deflated balloon and guidewire are removed and the patient is transferred to the recovery area. The patient is observed for five to six hours since serious

complications, such as perforation, will usually become clinically apparent within this time period (eg, tachycardia, persistent chest pain, subcutaneous emphysema) [9-12]. If recovery is uneventful, the patient is subsequently discharged. (See 'Complications' below.)

Dilation has also been performed using a hydraulic balloon dilation catheter (EsoFlip, Medtronic) [13]. The EsoFlip is a 7F, 230 cm long catheter with an 8 cm tapered nylon balloon with a maximum diameter of 30 mm. This catheter is distinct from the functional lumen imaging probe (FLIP) catheter-based device that is used for evaluating the mechanical properties of a specific area of the gastrointestinal tract (eg, esophagus). (See "Functional lumen imaging probe (FLIP) for adults with esophageal disorders", section on 'Equipment'.)

The EsoFlip catheter is typically advanced alongside the endoscope over a guidewire for direct visualization. In a pilot study including 10 patients, dilation was technically feasible without complications. The one-week response rate was 90 percent, while the three-month response rate dropped to 70 percent. In contrast to PD, use of a hydraulic balloon dilation does not require fluoroscopic guidance [14]. In a subsequent study including 28 patients with achalasia, dilation with EsoFlip was associated with improvements in Eckardt score and in esophageal emptying time [15]. Larger, long-term studies need to better evaluate the efficacy and safety of hydraulic balloon dilation in the treatment of achalasia.

Efficacy of PD — Approximately 71 to 90 percent of patients respond initially to PD [16-20]. In a pooled analysis, dilation with 30 mm, 35 mm, and 40 mm balloon diameters resulted in symptomatic relief in 74, 86, and 90 percent of patients, respectively, with an average follow-up of 1.6 years [2]. However, the definition of clinical success has varied in some observational studies. For example, clinical success included patients who required repeat dilation in some studies. We counsel patients that approximately 50 percent of patients undergoing PD for achalasia will subsequently require repeat dilation.

In addition, PD may not be equally effective for relieving all symptoms of achalasia. In one report, for example, PD had little effect on chest pain, which is present in approximately 40 to 60 percent of patients with achalasia [21]. In another study, chest pain continued after PD in approximately half of the patients who initially complained of this symptom [22]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical features'.)

Short- to medium-term results — Short- to medium-term results with PD have been described in observational studies and clinical trials. Small (7 to 29 patients) prospective studies of PD using Rigiflex balloons reported success rates of 53 to 93 percent, but most involved less than two years of postprocedure follow-up [23,24]. Two larger prospective studies of approximately 50 patients each with longer follow-up had less favorable results, with a

remission rate of 26 to 40 percent after four years or more [25,26]. A prospective study of 77 patients had better results, with 70 percent of patients in remission after a median of 5.6 years of follow-up (range 3 to 10.7 years) [19]. In a randomized trial including 201 patients with achalasia who underwent either PD (with at least two graded dilations of 30 mm and 35 mm diameter, respectively, and an additional dilation to 40 mm on the basis of symptoms) or laparoscopic Heller myotomy, rates of therapeutic success (ie, postintervention Eckardt score ≤3) after a mean duration of 43 and 60 months following PD were 90 and 82 percent, respectively [20,27]. (See 'Comparative studies' below.)

PD has also been studied in children with achalasia. In a prospective study of 24 children with achalasia who were followed for a median of six years (range two to seven years), the overall success rate following PD (up to three sessions) was 87 percent [28]. Older children were more likely to respond to PD than younger children.

Long-term (>10 year) results — Achalasia is a chronic disease, and patients may need to be followed for more than a decade to judge the success of treatment, while few studies have addressed the outcome of PD after 10 years or more. Complete symptom resolution has been described in some patients followed for as long as 10 to 25 years [9,29,30]. Data are conflicting, however, with respect to the likelihood of maintenance of long-term remission:

- A retrospective study of 153 patients found that, after five years, 76 percent of patients reported good to excellent symptom outcomes [31]. Of the 35 patients with 15 or more years of follow-up, 18 (51 percent) reported good or excellent outcomes by the end of follow-up. The median time to symptom recurrence in this study was 11 years.

- In a retrospective report of 126 patients, 115 (91 percent) improved after one to three sessions of PD. The median dysphagia-free duration was 60 months [16].

- In a prospective study, 54 consecutive patients were followed every two years for a period of 10 years, with a mean follow-up of 14 years [26]. The remission rate at five years after a single PD was 40 percent. Among the 21 patients in remission at five years, 18 remained in remission for an additional 10 years. Thus, patients whose symptoms were well controlled for five years were likely to continue to do well.

- A retrospective study included 228 patients who had an initial response to PD (defined as being symptom-free at 12 months following the first PD) [32]. During follow-up, the estimated relapse-free survival rates were 18 percent by 2 years, 41 percent by 5 years, and 60 percent by 10 years. During follow-up, additional treatments (PDs, myotomy, botulinum toxin injections) were performed in 34 percent of 163 patients for whom data were available. Overall, after a mean follow-up of 9.3 years, the long-term success rate was

71 percent (68 percent for those who had no additional treatment, 79 percent for those who had interval PD, and 77 percent for those who received other interval treatments).

- A cohort study of 107 patients who were treated with PD with a median follow-up duration of 13.8 years found that symptomatic response to a single dilation decreased over time from 64 percent at two years to 36 percent at 20 years [33].

Subsequent dilations — The value of repeat dilations after the first relapse has been difficult to evaluate objectively. In a prospective study of 54 patients cited above, only 35 percent of patients who received three dilations were in remission after five years [26]. However, a retrospective study of 150 patients suggested that repeated dilations may help improve long-term remission rates [17]. In that study, 137 patients (91 percent) went into remission. Among the 25 patients who attained remission after one session of PD and did not undergo repeat PD, 67 percent were in remission at five years and 50 percent at 10 years. By contrast, the 112 patients who received repeated dilations as needed for recurrent symptoms (an "on-demand" approach) had remission rates of over 90 percent at 10 years. Apart from the retrospective nature of this study, the higher response rate may also have been due to an older patient population. Studies have shown that older age is predictive of a better response to PD. (See 'Predictors of outcome' below.)

The results discussed above are from studies in which "graded" or "on-demand" dilations (that is, guided by symptom recurrence) were performed. A less popular regimen (the "progressive" method) practiced in Europe consists of a series of progressively larger dilations on the same or successive days until manometric (eg, lower esophageal sphincter pressure <15 mmHg) and/or radiographic criteria are met. A retrospective study of 209 patients who underwent PD by this method found that the response to a single series of dilations was 66 percent at six years. Forty-nine patients with recurrent symptoms underwent a second series of dilations 6.5 years later with a 65 percent long-term success rate [22].

Data have suggested that a graded approach (ie, initial 30 mm diameter balloon dilation, followed by elective dilation with larger balloons for persistent symptoms) was associated with better outcomes. In a meta-analysis of 10 studies including 643 patients with achalasia, symptom-driven dilation series were associated with higher rates of clinical remission compared with a predefined dilation series (86 versus 75 percent) [34]. While clinical success rates at six months were higher with dilation using a 40 mm diameter balloon compared with 30 mm or 35 mm balloons (90 versus 79 and 81 percent, respectively), larger diameter balloons were associated with higher rates of esophageal perforation.

Predictors of outcome — The two strongest predictors of outcome following PD are postdilation LES characteristics and age [16,26,30,35]. In addition, patient sex and achalasia subtype may also predict the response to PD:

- LES characteristics – A postdilation decrease in LES pressure to approximately 10 mmHg has been suggested as a reasonable goal of PD [30]. The value of achieving this goal was supported in a prospective study of 54 patients who were followed for 10 years [26]. Patients who achieved a postdilation pressure of less than 10 mmHg were much more likely to be in remission during follow-up compared with those with higher LES pressures (100 versus 23 percent). Higher postdilation distensibility of the esophagogastric junction has also been associated with a better treatment response compared with lower distensibility [36].

  The significance of pretreatment LES pressure with regard to long-term response is unclear. Most studies have found that pretreatment LES pressure does not influence response rates [16,37,38]. However, one study of 62 patients found that a pretreatment LES pressure >50 mmHg was associated with a poor response [18].

- Patient age – Data have suggested that younger age has been a predictor of poor response to PD [17,26,27,35,39,40]. As an example, in a prospective series of 54 patients with achalasia who underwent PD, younger age (<40 years) was associated with lower rates of remission compared with older patients (16 versus 58 percent at five years) [26]. A subsequent meta-analysis also identified younger age as a risk factor for requiring repeat therapy [41].

- Female sex – Female sex has been implicated as a predictor of more favorable PD treatment response [16,42]. In a retrospective study of 49 men and 16 women, young men treated with a 3 cm balloon required repeat treatment more frequently than young women (hazard ratio 1.65) [42]. The authors concluded that young men may benefit from an initial PD with a 35 mm balloon.

- Achalasia subtype – Type II achalasia by high resolution manometry has been associated with good response to PD [43,44]. Using high-resolution manometry, achalasia has been categorized into subtypes that may influence the treatment response (figure 1) [45] (see "High resolution manometry", section on 'Disorders of EGJ outflow obstruction'):

  - Type I (classic achalasia) is defined by no pressure generation in the esophagus

  - Type II (with pressurization) has at least 20 percent of swallows with a pattern of panesophageal pressurization

- Type III (spastic achalasia) has at least 20 percent of swallows with a shortened distal latency, a manometric variable associated with contractile speed

PD has been increasingly reserved for patients with type II achalasia. (See "Overview of the treatment of achalasia", section on 'Choice of treatment'.)

It should be noted that older studies used diagnostic classifications based on conventional manometry. As an example, patients with a diagnosis of vigorous achalasia by conventional manometry may be classified as either type II or type III achalasia subtypes by high-resolution manometry.

Special populations

Patients who failed myotomy — PD has been studied as a treatment option in patients who have failed surgical myotomy for achalasia or who have had symptomatic recurrence following surgical myotomy. The response to dilation in patients who have failed myotomy is not as good as the response seen in patients who are treatment naïve. However, we typically use PD for patients who failed surgical myotomy rather than repeating surgery, and this approach has been supported by society guidelines [46]. In one report, 22 of 139 patients undergoing PD had failed prior surgical myotomy [47]. A symptomatic response was seen in 50 percent of these patients compared with 74 percent of previously untreated patients. A second study looked at 27 patients who underwent PD for symptom recurrence after surgical myotomy [48]. At 12 months, 24 patients (89 percent) had responded. Relapse rates at two, three, and four years were 16, 25, and 42 percent, respectively.

Concern had been raised that PD following myotomy may increase the risk of perforation. However, in these two studies, none of the patients who had undergone prior surgical myotomy developed esophageal perforation with PD [47,48].

Patients who failed botulinum toxin injection — PD appears to be safe in patients who have previously received botulinum toxin (BT) injection, and some authorities have advocated combination therapy with PD and BT injection.

The efficacy of combined therapy was evaluated in a randomized trial in which 90 patients with achalasia were assigned to BT injection, PD, or both BT injection and PD [49]. The response rate at two years was higher with combination therapy (57 percent versus 14 percent with BT injection and 36 percent with PD).

A second randomized trial comparing combination therapy with PD alone found a nonstatistically significant difference in remission rates at one year (77 versus 62 percent) [50].

Additionally, a third randomized trial comparing PD plus BT with PD alone found a nonsignificant trend toward greater five-year remission rates for the combined therapy (69 versus 50 percent; p = 0.07) [51].

Patients who are pregnant — In women who are pregnant, the short-term efficacy of PD and surgical myotomy are similar, but PD is associated with a much lower risk of complications. As a result, PD should be attempted before surgical myotomy during pregnancy [52].

Complications

Esophageal perforation — Esophageal perforation occurs in approximately 3 to 5 percent of patients in most series, although the range varies from 0 to 21 percent [53-56]. In one series from a high-volume center that included 272 PDs in 198 patients, only one patient had a perforation [56]. Perforations usually occur during the first dilation session, tend to be small, and are typically located above the cardia along the left side of the esophagus, where there is an anatomic area of weakness. As an example, the European Achalasia Trial initially started dilations with the 35 mm balloon. Among the initial 13 patients, the perforation rate was 31 percent, prompting the investigators to amend the protocol to start dilations using the 30 mm dilator [20].

Patients with esophageal perforation usually present within a few hours after dilation. Findings that raise concern about perforation include tachycardia and persistent chest pain following the procedure that lasts for more than four hours [9]. When perforation is suspected, we obtain an esophagram using water-soluble contrast to avoid the risk of barium-related mediastinitis. Although some endoscopists routinely obtain a post-procedure esophagram, most endoscopists obtain an esophagram only for patients in whom perforation is suspected. (See 'Technique' above.)

Several studies have evaluated risk factors for perforation. These include high-amplitude esophageal contractions on manometry before the procedure [57] and instability of the balloon during insufflation [58]. Neither of these predictors has been validated.

The optimal management of esophageal perforation following PD has not been established. Perforations can often be managed with conservative treatment such as antibiotics and parenteral nutrition [55,58-60]. The role of endoscopic therapy in treatment of esophageal perforations has yet to be determined. Esophageal stenting and closure with an over-the-scope clip have been described [61,62]. However, it is difficult to predict how a given patient will respond. Most patients do well after surgical repair. Thus, many authorities advocate surgery in low-risk patients as soon as the diagnosis is confirmed, regardless of the size of the perforation. (See "Complications of endoscopic esophageal stricture dilation".)

Clinical deterioration or the presence of free-flowing contrast material into the mediastinum requires immediate thoracotomy and repair. Videothoracoscopic and endoscopic repair have also been performed in this setting [63,64]. (See "Complications of endoscopic esophageal stricture dilation".)

Other complications — Other complications of PD include bleeding, intramural hematomas, esophageal mucosal tears, and diverticula at the gastric cardia [9,17,58]. Postprocedural fever usually resolves spontaneously without antibiotics. Approximately 15 percent of patients complain of severe postprocedural chest pain that is self-limited. Chest pain following the procedure that lasts for more than four hours is suggestive of possible esophageal perforation [9,17]. (See 'Esophageal perforation' above.)

Despite PD-induced disruption of the LES, which is the principal barrier to gastroesophageal reflux, gastroesophageal reflux disease is uncommon after PD. A review of 1902 patients found an overall incidence of 2 percent [53].

BOTULINUM TOXIN INJECTION

Botulinum neurotoxin type A is a potent inhibitor of the release of acetylcholine from nerve endings and has been used successfully to treat certain spastic disorders of skeletal muscle such as blepharospasm and torticollis. It is also used in the treatment of spastic disorders of smooth muscle, including achalasia.

The idea of using botulinum toxin (BT) in achalasia stems from an understanding of the pathophysiology of achalasia. Achalasia is caused by the selective loss of inhibitory neurons, which results in unopposed excitation of the lower esophageal sphincter (LES) by cholinergic neurons [65-67]. BT can reduce LES pressure by selectively blocking the release of acetylcholine from presynaptic cholinergic nerve terminals in the myenteric plexus, thereby restoring the balance between inhibitory and excitatory neurotransmitters [68,69].

In addition to being used as a treatment for achalasia, a response to BT injection has been used to support the diagnosis of achalasia in patients in whom the diagnosis is uncertain based upon manometry [70]. (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Esophageal manometry'.)

Technique for BT injection — BT is injected during a routine upper endoscopy using a standard sclerotherapy needle that is passed through the accessory channel of the endoscope. As with pneumatic dilation (PD), a thorough endoscopic examination is performed, with particular attention given to the cardia, where malignancy can simulate achalasia (called

pseudoachalasia). (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Upper endoscopy'.)

The most common method for delivering BT involves visual estimation of the location of LES and injection of 1 mL aliquots (20 to 25 units BT/mL) into each of four quadrants approximately 1 cm above the Z-line. The Z-line is the squamocolumnar junction, which corresponds to the gastroesophageal junction in the absence of Barrett's esophagus.

The use of endoscopic ultrasound to identify the LES has been suggested as an aid for guiding injection, but there is no evidence that this improves efficacy. Manometrically guided BT injection by means of a double-channel endoscope has also been described [71]. This may theoretically permit more precise targeting of the LES. However, absolute precision is probably not necessary since BT diffuses for a limited distance in tissue [72].

Patients are discharged from the endoscopy unit after routine post-sedation requirements have been met and are allowed to eat later in the day. An improvement in symptoms is usually observed after 24 hours, although peak effects occur later in some patients.

Several formulations of BT are available. A comparison between Botox 100 units and Dysport 250 units showed similar efficacy at up to six months of follow-up [73].

Efficacy of BT injection — Initial response rates to BT injection range from 70 to 90 percent, but many patients relapse within several months [74-84]. Thus, BT injection is generally regarded as a short-term intervention for patients with achalasia who are not good candidates for more definitive therapy because of comorbidities or advanced age [1,2].

The vast majority of studies have reported an improvement in objective parameters, with the most common being a reduction in resting LES pressure, generally averaging around 40 percent [23,74,78,85,86]. Although less commonly reported, radiographic or scintigraphic measures also improve [74,87,88].

Short-term results (<5 years) — In a systematic review, relapse rates of greater than 50 percent were seen in many studies within 6 to 12 months following a single treatment session [89]. Better results were obtained in studies that used multiple treatment sessions, with clinical benefit seen in 60 to 85 percent of patients at two years.

The following studies illustrate the range of findings:

- In a study of 60 patients with idiopathic achalasia who were treated with BT injection, 70 percent had significant symptom improvement at one month following a single treatment [77]. Among the 33 patients with one-year follow-up, 36 percent continued to have a good

or excellent response, whereas 39 percent had undergone a subsequent treatment (repeat injection, PD, or myotomy). A response was seen in six of seven patients who received a second injection of BT.

- A randomized trial suggested that the dose of BT and the dosing schedule may predict a response to treatment [84]. The trial included 118 patients who were randomly assigned to receive one of three doses of BT (50, 100, or 200 units). Patients assigned to the 100-unit dose were reinjected with an additional 100 units after 30 days. At 12 months, patients who received the two-dose schedule of 100 units were more likely to be in remission (80 versus approximately 55 percent for the other two groups). On multivariate analysis, independent predictors of response included the two-dose regimen and vigorous achalasia (a manometric feature that is no longer included in the manometric criteria for achalasia subtypes). (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Esophageal manometry'.)

The durability of the response to BT may be improved by multiple treatment sessions, similar to the approach for other conditions (eg, dystonia) (see "Treatment of dystonia in children and adults"). Anecdotally, however, it appears that the response to BT injections for achalasia is often less robust with subsequent injections. Antibodies to BT have been detected in patients who were secondary treatment failures for various indications. In one study, antibodies were found in 45 percent of patients who were secondary nonresponders [90]. Despite concerns about neutralizing antibodies, one group was able to maintain clinical remission with repeat BT injections every 10 months in 43 of 57 patients (75 percent) for four years [81].

Predictors of response — The main predictors of a favorable outcome are older age and the presence of vigorous achalasia (a manometric feature that is no longer included in the manometric criteria for achalasia subtypes). This was illustrated in a study of 31 patients who were treated with BT and were followed prospectively for a median of 2.4 years [83]. A response beyond three months was more likely in patients older than age 50 (82 versus 43 percent) and in patients with vigorous compared with classic achalasia (100 versus 52 percent). (See "Achalasia: Pathogenesis, clinical manifestations, and diagnosis", section on 'Esophageal manometry'.)

Factors that are not reliable predictors of a response to BT injection include patient sex, duration of illness, mean number of previous dilations, characteristics on conventional manometry (except for vigorous achalasia), and initial symptom scores [75,77,83].

Complications of BT — The low dose of BT used for treatment of achalasia has virtually no risk of causing generalized neuromuscular blockade. (See "Botulism".)

Reported complications include postprocedural transient chest pain (with rates ranging from 5 to 25 percent) and heartburn (5 percent) [91]. Esophageal wall injury and paraesophageal tissue inflammation are rare [92]. Other rare complications have primarily been described in case reports:

- Nonfatal mediastinitis following BT injection [93,94].
- Esophageal mucosal ulceration and sinus tract formation [95].
- Pneumothorax requiring drainage [96].

Long-term experience with BT injection in the gastrointestinal tract is limited, but it appears safe. Support for this conclusion comes from the observation that no significant mucosal or submucosal changes were seen during endoscopic ultrasound following treatment in a study of 18 patients [97]. Similarly, a retrospective analysis of 661 esophageal BT injections found that the most common complications were mild and infrequent (chest pain and epigastric pain), with younger patients at slightly greater risk [91].

COMPARATIVE STUDIES

A number of studies and meta-analyses have compared the efficacy of pneumatic dilation (PD), botulinum toxin injection (BT), surgical myotomy, and peroral endoscopic myotomy (POEM) [20,46,78,85,87,98-105]. The choice of treatment is informed by several factors including the patient's surgical risk, achalasia subtype, patient preference, and local institutional endoscopic and surgical expertise, and these issues are discussed in more detail separately. (See "Overview of the treatment of achalasia", section on 'Treatment approach'.)

PD versus BT injection — Data have suggested that PD resulted in higher rates of long-term remission than BT [98,102]. In a meta-analysis of seven trials including 178 patients treated for achalasia, PD resulted in higher remission rates at 12 months compared with BT injection (73 versus 38 percent; risk ratio 1.88, 95% CI 1.35-2.61) [102].

PD versus laparoscopic myotomy — PD and laparoscopic Heller myotomy are both treatment options for patients with achalasia, while data comparing the efficacy of the interventions have been mixed [103,104]. In a 2019 meta-analysis of four randomized trials including 404 patients with achalasia, there was no significant difference in symptom response rates for PD compared with surgical myotomy at two years and at five years postintervention. Rates of gastroesophageal reflux were not significantly different; however, the esophageal perforation rate was higher in patients who had PD (5 versus 1 percent) [104]. In a 2013 meta-analysis of three randomized trials including 346 patients with one-year follow-up, the rate of symptom

response was lower for graded PD compared with surgical myotomy (76 versus 86 percent), while the adverse event rate was higher for PD (4.8 versus 0.6 percent) [103]. However, there were no significant differences in postprocedure lower esophageal sphincter pressure, rate of gastroesophageal reflux, and quality of life.

However, a number of factors require consideration when interpreting these comparison data including variations in protocols for performing PD, burden of treatment (eg, possible need for repeat PD, procedure recovery time), long-term risk of gastroesophageal reflux disease, availability of endoscopic and surgical expertise, and need for emergency surgical repair if perforation with PD occurs. (See 'Subsequent dilations' above.)

PD versus endoscopic myotomy — Initial data have suggested that POEM resulted in higher rates of treatment success than PD [46], and efficacy of POEM for primary achalasia is discussed separately. (See "Peroral endoscopic myotomy (POEM)", section on 'Outcomes of POEM for achalasia'.)

BT injection versus laparoscopic myotomy — BT injection typically has not resulted in long-term benefit. In a meta-analysis of two trials that compared BT injection with laparoscopic myotomy, there was no significant difference in rates of symptom recurrence during the first six months of follow-up [98]. However, after one year of follow-up, BT injection resulted in lower rates of response (65 versus 83 percent). In addition, patients treated with BT had more frequent relapses and a shorter time to relapse.

IMPACT OF ENDOSCOPIC TREATMENT ON SUBSEQUENT MYOTOMY

In animal models, both pneumatic dilation (PD) and botulinum toxin (BT) injection induce acute and chronic esophageal inflammation, with areas of increased fibrosis in the muscle [106]. This has led to concern regarding the effects of prior PD or BT treatment on the success of subsequent surgery. (See "Surgical myotomy for achalasia".)

The available data in humans are conflicting. Some studies suggest that prior endoscopic therapy decreases the efficacy of subsequent myotomy and may increase complication rates [107-110]. However, because the studies were not randomized, it is not possible to determine whether the lower efficacy was due to a true effect or to the inclusion of patients in the myotomy studies following endoscopic treatment who were refractory to any form of treatment.

Other nonrandomized studies have shown similar surgical outcomes with regard to efficacy and/or complications for patients who had previously received endoscopic therapy compared

with patients undergoing laparoscopic myotomy or peroral endoscopic myotomy as initial therapy [111-115].

Regardless, definitive sphincter-disrupting therapy (ie, myotomy) is typically performed for most patients early in the course of disease rather than an indefinite series of BT injections. (See "Overview of the treatment of achalasia", section on 'Choice of treatment'.)

FOLLOW-UP

Because there is no cure for achalasia, regular follow-up is required. We evaluate patients within one month following endoscopic therapy. Patients who remain symptomatic are offered repeat dilation.

Patients are usually referred to surgery if three consecutive pneumatic dilations do not provide symptom resolution. Consideration for surgical referral should also be made in patients with early symptom recurrence following pneumatic dilation (PD). (See 'Efficacy of PD' above.)

The follow-up of patients treated with botulinum toxin (BT) depends upon the indication for BT. As noted above, we typically reserve BT injections for patients who are (1) not surgical or PD candidates, (2) reluctant to undergo surgery or PD, or (3) patients with atypical presentations of achalasia to help guide therapy. In the first scenario, we monitor patients closely for recurrence of symptoms and offer repeat BT injections until they become surgical candidates or until BT loses efficacy if they remain poor surgical candidates. In the second scenario, we monitor the patient closely at one and four months after therapy. If there is no response after two BT injections, we encourage proceeding to either PD or surgery. In the third scenario, patients who respond to BT injection are referred for surgery or PD if the patient is reluctant to have surgery.

Patients who do well with the above therapies, especially BT injection, require close follow-up to monitor for symptom recurrence. Patients who had BT injection are followed one month after therapy and subsequently every three months until symptom recurrence. Patients who had PD are followed-up at 1, 3, 6, and 12 months after therapy and every four to six months thereafter. In addition to recurrence of dysphagia, particular attention is paid to the development of reflux symptoms, for which proton pump inhibitor therapy is prescribed empirically. However, patients who have had either BT or PD receive long-term acid suppression therapy only if they develop reflux symptoms or pH testing demonstrates acid reflux [46]. (See "Esophageal multichannel intraluminal impedance testing", section on 'Combined multichannel intraluminal impedance and pH'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Achalasia".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Achalasia (The Basics)")
- Beyond the Basics topics (see "Patient education: Achalasia (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Background** – Therapeutic options for achalasia include pneumatic dilation (PD), botulinum toxin (BT) injection, peroral endoscopic myotomy, and surgical myotomy. The approach to choosing among the different treatment options is discussed in detail elsewhere. (See "Overview of the treatment of achalasia".)
- **Endoscopic therapy with PD or BT for achalasia** – Endoscopic therapy with PD or BT injection for the treatment of achalasia has the advantage of being less invasive compared with surgery. While symptom recurrence is common with BT, in experienced hands, PD may have success rates similar to surgical myotomy, but may require repeat dilations in a significant number of patients (25 to 50 percent) along with a nontrivial risk of perforation. (See 'Efficacy of BT injection' above and 'Efficacy of PD' above.)

- Initial response rates of 70 to 90 percent are seen with BT injection, but many patients relapse within several months. Better results have been seen in studies that used multiple treatment sessions, with clinical benefit seen in 60 to 85 percent of patients at two years. (See 'Efficacy of BT injection' above.)

- The most common complications of BT injection are postprocedural transient chest pain (up to 25 percent) and heartburn (5 percent). (See 'Complications of BT' above.)

- Approximately 70 to 90 percent of patients respond initially to PD, but many patients subsequently relapse. One-third to one-half of patients treated with PD will require at least one additional dilation, and a subset of these patients will require surgery. (See 'Efficacy of PD' above.)

- Complications of PD include esophageal perforation, bleeding, intramural hematomas, esophageal mucosal tears, diverticula of the gastric cardia, and gastroesophageal reflux. (See 'Complications' above.)

- **Myotomy** – Myotomy has the advantage of offering a more definitive therapy for managing the symptoms of achalasia, but it is more invasive than PD and puts patients at increased risk for reflux (particularly in the case of endoscopic myotomy) and other complications. (See "Surgical myotomy for achalasia" and "Peroral endoscopic myotomy (POEM)".)

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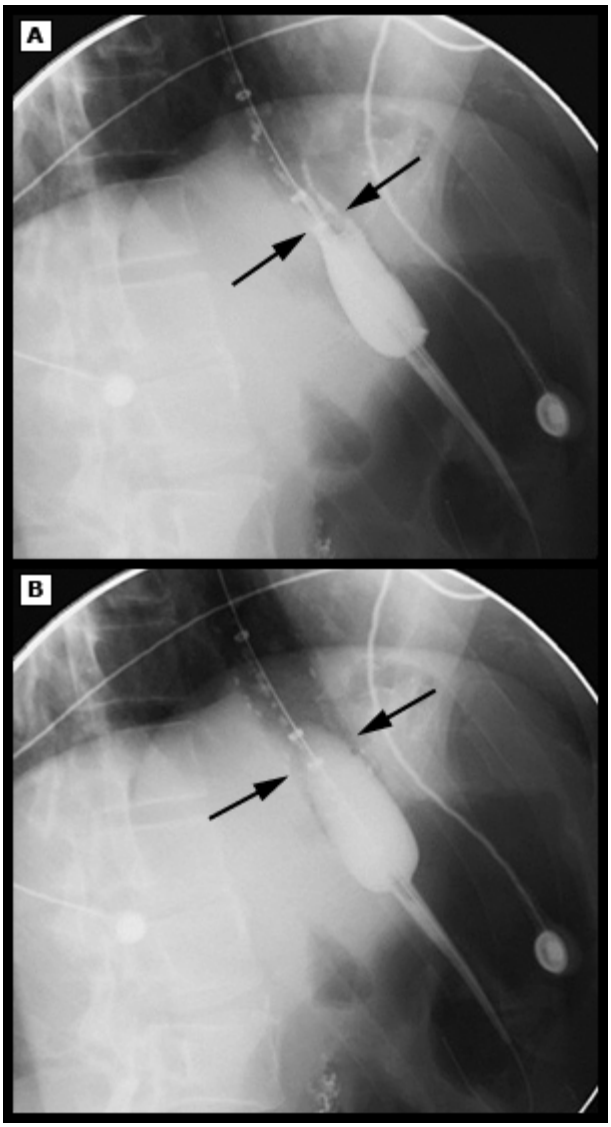
Topic 2245 Version 36.0

GRAPHICS

Pneumatic dilation for the treatment of achalasia



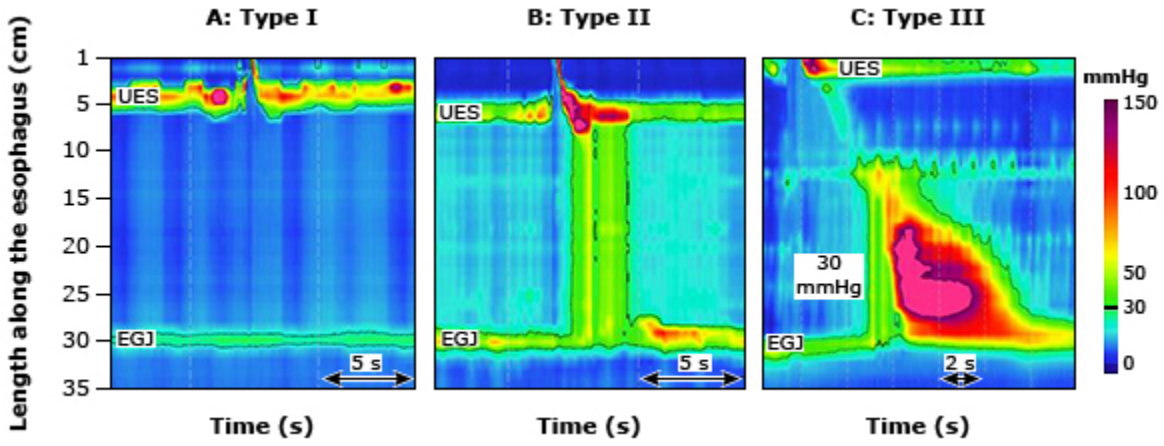
(A) Arrows indicate the "waist" of the balloon as it is being insufflated with air and pre-injected with water-soluble contrast.

(B) Obliteration of the waist with the balloon fully inflated.

Courtesy of Linda Nguyen, MD.

Graphic 66408 Version 5.0

Esophageal pressure topography plot of achalasia subtypes in the Chicago Classification



In each case, the 30 mmHg isobaric contour is highlighted in black and there is impaired EGJ relaxation evident by the EGJ never relaxing to less than 30 mmHg in any panel. With type I achalasia, there is minimal contractile activity between the UES and EGJ. Type II is defined by ≥20 percent of swallows (supine posture, 5 mL water) with panesophageal pressurization to ≥30 mmHg. With type III, there is ≥20 percent of swallows with either premature contractions or fragments of peristalsis.

EGJ: esophagogastric junction; UES: upper esophageal sphincter.

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Graphic 86439 Version 2.0

Contributor Disclosures

Pankaj J Pasricha, MD No relevant financial relationship(s) with ineligible companies to disclose. **Nitin K Ahuja, MD, MS** Grant/Research/Clinical Trial Support: Nestle [Irritable bowel syndrome]; Vanda Pharmaceuticals [Gastroparesis]. Consultant/Advisory Boards: Ardelyx [Constipation]; GI Supply [Constipation]; GlaxoSmithKline Consumer Healthcare [GERD]; Takeda [Constipation]. All of the relevant financial relationships listed have been mitigated. **Nicholas J Talley, MD, PhD** Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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