Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Endoscopic Management of Achalasia

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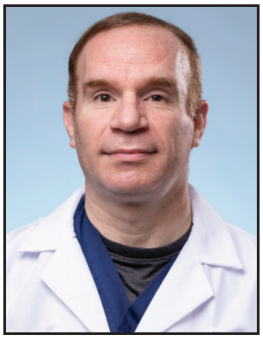

Douglas G. Adler

INTRODUCTION

Achalasia is a rare, chronic motility disorder of the esophagus with a worldwide prevalence of 1.8 to 12.6 per 100,000 people.[1] In the US, a study published in 2022 reported incidence and prevalence rates of 10.5 and 18.0 per 100,000 people, respectively.[2] Individuals of all races and sex are equally affected, but incidence increases with advancing age.[1] This review examines the efficacy and safety of endoscopic treatment options for achalasia.

Etiology

The pathogenesis of achalasia is poorly understood, complex, and likely multifactorial. Affected patients have impaired function of inhibitory neurons in the distal esophageal myenteric plexus leading to a decrease in inhibitory vasoactive intestinal peptide (VIP) and nitric oxide (NO) and unopposed excitatory acetylcholine within the lower esophageal sphincter (LES) and distal esophagus. This results in impaired relaxation of the LES and diminished, or absent, esophageal peristalsis.[1,3,4]

Achalasia is most commonly idiopathic with the leading hypothesis suggesting an autoimmune process in genetically predisposed patients or those with a preceding viral illness.[5,6] Secondary etiologies include malignancy, specifically small cell lung cancer via paraneoplastic secretion of antineuronal antibodies, and Chagas disease from *Trypanosoma cruzi* infection.[5] Chagas disease is highly common in endemic regions such as Central and South America with secondary achalasia occurring in 7-15.5% of patients with Chagas disease in these regions.[7]

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Symptoms

Patients present with progressive solid and liquid dysphagia, often accompanied by chest pain (50% of patients), regurgitation (75%), weight loss (60%), and/or heartburn (40%) which leads many patients to first be diagnosed with gastroesophageal reflux disease (GERD).[1,3,8,9] Symptoms are quantified using the Eckardt symptom scoring system with composite scores ranging from 0-12 based on frequency of dysphagia (0-3), regurgitation (0-3), retrosternal pain (0-3), and weight loss (0-3).[10] In most studies, post-treatment composite scores ≤3 indicate clinical remission whereas composite scores >3 indicate treatment failure.

Diagnosis

Many patients undergo upper endoscopy which is important to rule out pseudoachalasia from mechanical obstruction or malignancy and may reveal a tight, puckered gastroesophageal junction (GEJ) with saliva and/or food retention.[1] Barium esophagram may be performed revealing esophageal dilation with a classic "bird beak" appearance.[1] However, the gold standard diagnostic modality which provides important prognostic and treatment implications is high-resolution esophageal manometry.[1]

Using high-resolution esophageal manometry, patients are classified into 3 subtypes according to the Chicago Classification.[11] All three achalasia subtypes share the disorder's hallmark of aperistalsis with impaired GEJ relaxation but vary by their dominant pattern of esophageal body contractility.[11] Type I achalasia occurs in 20-40% of cases and is the most severe form characterized by low or absent esophageal pressurization.[1,11,12] Type II achalasia occurs in 50-70% of cases and is characterized by rapid panesophageal pressurization >30mmHg.[1,11,12] Type III achalasia occurs in 5-10% of cases and is characterized by rapid spastic contractions.[1,11,12] While all the same disorder, this classification is helpful when determining the best treatment approach.

Botulinum Toxin Injections

Technique

Botulinum toxin injections (BTI) induce local, transient, and partial paralysis of the LES to decrease sphincter tone and improve esophageal emptying.[13] Botulinum toxin (BTX) works by inhibiting the release of acetylcholine into neuromuscular junctions, thereby preventing muscle contraction at the LES.[13] The three A1 BTX subtypes, abobotulinum, incobotulinum, and onabotulinum, are the most studied and, therefore, most commonly administered BTX formulations.[13]

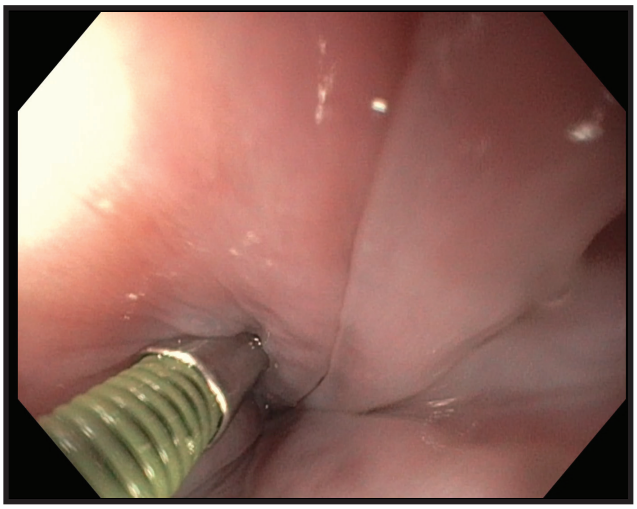

Figure 1. Endoscopic Botox injection into the lower esophageal sphincter in a patient with achalasia

To perform BTI, a standard endoscopic injection needle is used to inject 80-100U (20-25U in each quadrant) of BTX approximately 1cm proximal to the Z-line under endoscopic visualization.[1,13,14] (Figure 1) In general, injections of BTX produce symptom relief for several months at a time. BTX injections can be repeated every 3-6 months as needed. The procedure is usually performed on an outpatient basis, taking minutes to complete on average.[14]

Efficacy

Pasricha et al. performed the first RCT in 1995 with 21 patients showing a significant decrease in symptom score (5.4 vs 0.5; p=0.001) and LES pressure (33% decrease vs 12% increase; p=0.02) between BTX and placebo groups, respectively.[15] Subsequent studies have shown good short-term efficacy with clinical success observed in 73.7-90.5% of patients at 1 month.[15,16,17,18,19] Unfortunately, symptom recurrence remains a major problem. Campos et al. highlighted this in a meta-analysis of 9 studies with 315 patients which

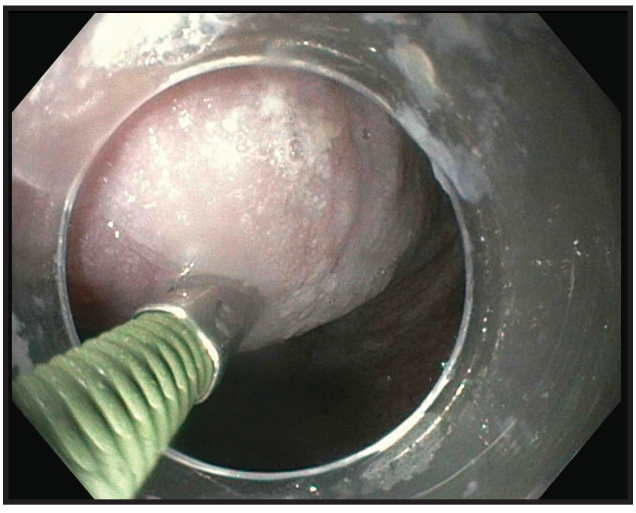

Figure 2a. Submucosal injection into esophagus prior to mucosotomy

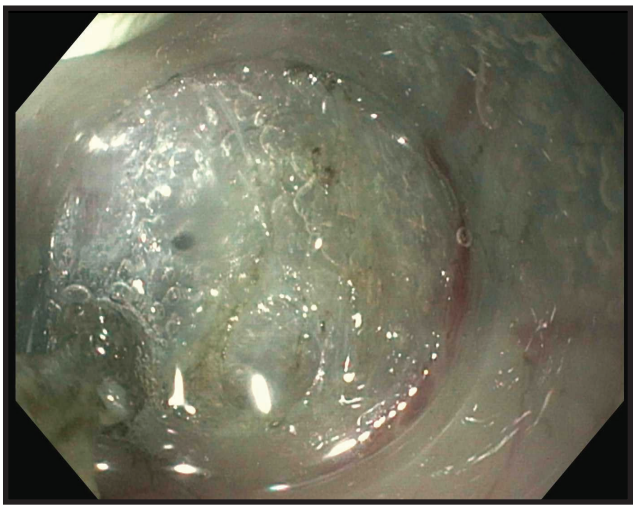

Figure 2b. Submucosal space in esophagus

revealed a progressive decline in symptomatic improvement with 78.7%, 70%, 53.3%, and 40.6% of patients in remission at 1, 3, 6, and 12 months, respectively.[17] Because of this, BTI is only recommended as first-line treatment in older patients who have decreased life expectancy and/or are poor candidates for more invasive endoscopic techniques and surgery.[1]

Adverse Events

No serious adverse events were reported across multiple studies.[15,18,19,20,21] Patients may experience minor adverse events such as transient post-procedural chest or epigastric pain as reported by D'Onofrio et al. and Annese et al.[16,19]

There is potential for fibrosis to develop at the GEJ following BTI with potentially important implications for future therapeutic interventions. According to Patti et al., patients who did not respond to BTI have a lower risk for developing fibrosis and responded well to subsequent surgical myotomy.[22] Conversely, patients who initially responded to BTI but underwent subsequent surgical myotomy for relapse of symptoms experienced an increased number of perforations and failure rates, presumably due to BTI-induced scarring at the GEJ.[22,23] Interestingly, recent studies suggest efficacy and safety are not impacted by post-BTI fibrosis following subsequent peroral endoscopic myotomy (POEM).[24,25,26]

Pneumatic Dilation

Technique

Pneumatic dilation (PD) utilizes single-use balloon dilators to mechanically disrupt LES fibers, resulting in a widened LES orifice and improved esophageal emptying.[8] Becker et al.'s RCT with 35 patients compared high compliance balloons made of latex that expand with lower inflation pressures and low compliance balloons made of polyethylene that require higher pressures to expand and found no significant difference in outcomes.[27] Despite similar outcomes, low compliance balloon dilators have overtaken high compliance balloon dilators on the market because they allow for a more controlled dilation process. Commercially available options in the US include the Rigiflex II single use balloon dilator (Boston Scientific, Natick, MA, United States), Achalasia Over the Wire Balloon Dilator (Hobbs Medical, Stafford Springs, CT, United States), and Achalasia Balloon (Cook Medical, Winston Salem, NC, United States) with fully inflated balloon diameters ranging 30-40mm.[28]

To perform PD, a guidewire is positioned across the GEJ, and the uninflated balloon is passed over the wire until the midpoint of the balloon aligns with the LES.[18] If fluoroscopy is used, the

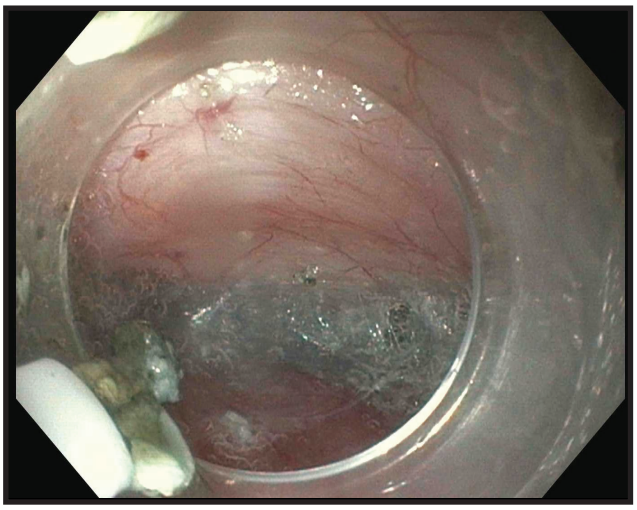

Figure 2c. View in the submucosal tunnel showing inner circumferential muscle fibers

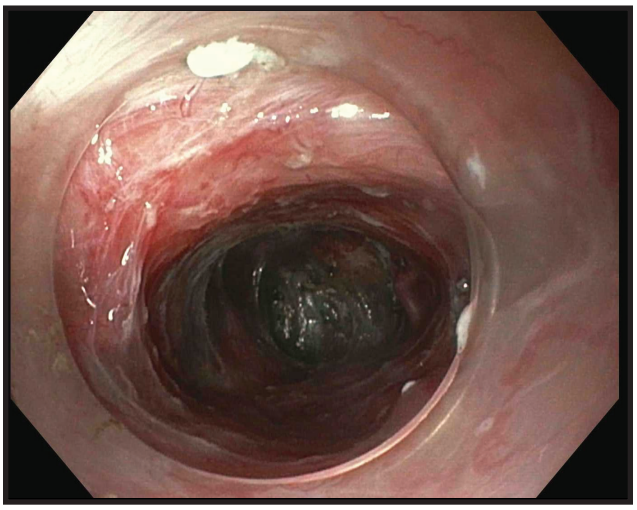

Figure 2d: Long view of completed submucosal tunnel

radiopaque ends of the balloon can be visualized to ensure adequate placement across the level of the diaphragm prior to inflation.[28,29] The next steps are operator-dependent, but the balloon is gradually inflated to 10-15 PSI and held in place for 15-60 seconds.[18,29,30,31,32] Khan et al. and Gideon et al. compared shorter inflation durations (6 and 15 seconds, respectively) to a 60-second inflation time and found no significant differences in efficacy or adverse events between groups.[29,33] In general, most patients are initially dilated using a 30mm diameter ballon, but serial dilations with 35mm or 40mm balloons may be required every few weeks until symptomatic relief is achieved.[31]

Efficacy

Leyden et al. performed a meta-analysis revealing symptom resolution in 80.7% (46/57) and 73.3% (55/75) of patients undergoing PD at 6 and 12 months, respectively.[34] van Hoeij et al.'s larger meta-analysis of 10 studies with 643 patients undergoing PD compared clinical success over time following single dilation with different balloon diameters (30mm, 35mm, and 40mm).[35] At 6 months, clinical success was observed in 81%, 79%, and 90% of patients following PD with 30mm, 35mm, or 40mm balloons, respectively.[35] At 12 months, clinical success was sustained in 77%, 70%, and 87% of patients, respectively.[35] This contrasts a single-institution prospective study published previously by Farhoomand et al. which showed dilation using a 30mm balloon dilator alone had a significantly lower 3-year success rate (37%; 95% CI 26-53) compared to serial dilation using 30mm followed by 35mm (76%; 95% CI 65-88) or 30mm followed by 35mm and 40mm (88%; 95% CI 80-97).[36]

Remission is more likely to be achieved in patients who are female, >40-45-years-old, and those with post-PD LES pressures <10mmHg, though this measurement is not commonly performed.[1,36,37] Farhoomand et al. identified high early failure rates (88% within 3 months) in young men treated with 30mm balloons.[36] Therefore, younger men may benefit from initial dilation with a larger balloon (35mm or 45mm) and/or serial PD.

Adverse Events

Minor adverse events include chest pain or reflux symptoms, but the major, life-threatening, and well-documented adverse event associated with PD is esophageal perforation. Perforation occurs in approximately 1.0-1.6% of patients undergoing PD.[30,34,35] van Hoeij et al. compared the risk of perforation based on balloon diameter and found a significantly ($p<0.027$) higher rate of perforation following use of 35mm balloons (3.2%; 9/282) compared to 30mm balloons (1.0%; 6/588).[35] However, the use of 40mm balloons surprisingly did not result in any adverse events, including esophageal perforation (0%; 0/62).[35] The reason behind this lower rate of perforation following use

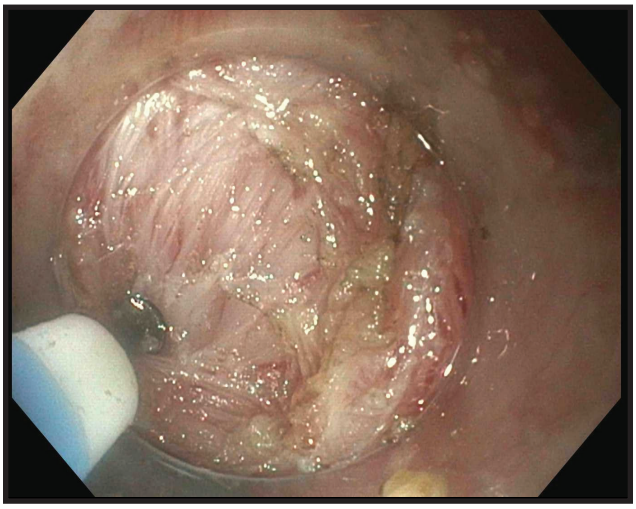

Figure 2e. Endoscopic myotomy showing inner circumferential muscle fibers being transected with outer longitudinal muscle fibers visible

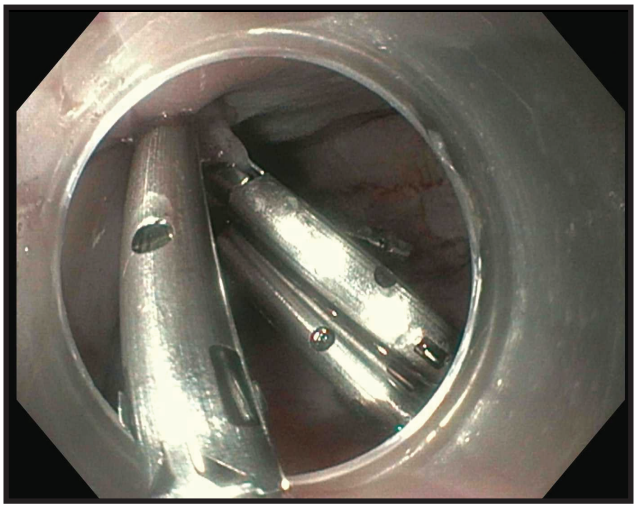

Figure 2f. Endoscopic closure of mucosotomy at completion of POEM procedure

of the largest balloon size is unclear. Perforations occurred significantly more after the initial PD compared to subsequent PD procedures (9.3% vs 0.97%, p=0.0017), and there was no correlation between inflation time or maximum balloon pressure and perforations.[35]

Because of the high risk for perforation, routine testing after PD has been debated, but the most recent ACG guidelines discourage performing post-PD gastrografin esophagrams unless there is clinical concern for perforation.[1]

Esophageal Functional Luminal Imaging Probe Dilation

Technique

Esophageal functional luminal imaging probe (EsoFLIP) dilation is a novel method of mechanically disrupting LES fibers in a more controlled manner than PD.[38] This FDA-approved device utilizes advanced technology to provide real-time measurements of intraluminal pressure and diameter at multiple points along the balloon catheter before, during, and after LES dilation.[38,39] The EsoFLIP ES-330 balloon catheter (Medtronic, Minneapolis, MN, United States) is commercially available in the US with a maximum inflated balloon diameter of 30mm.[39] Baumann et al. outline various step-by-step techniques to successfully perform EsoFLIP dilation.[38]

Efficacy

Very few prospective and retrospective cohort studies have been performed to date with short-term clinical success achieved in 52.9-85% of patients.[40,41,42,43,44] However, no individual study included more than 28 patients with achalasia. Therefore, larger prospective studies, including studies aimed at assessing long-term symptom relief, and randomized controlled trials are needed.

Adverse Events

Similar to post-PD patients, reflux symptoms (10.7-25% of patients) and transient chest pain (15%) were the most common adverse events encountered after EsoFLIP dilation.[40,41] Esophageal perforation occurred in 1.2% (1/85) of patients in these small studies.[40,41,42,43,44]

Peroral Endoscopic Myotomy

Technique

Peroral endoscopic myotomy (POEM) utilizes third-space endoscopy to treat achalasia. The concept of POEM was first outlined by Pasricha et al. in 2007 through experimentation on pigs and later introduced as a treatment option for individuals with achalasia by Inoue et al. in 2009.[45,46]

There are many variations to POEM, but in general, a mucosal entry site is made within the

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esophagus to expose the submucosal space. Once inside, a submucosal tunnel is created, extending a short distance past the GEJ. Then, circular LES muscle fibers are dissected until the endoscope can be easily passed through the GEJ to confirm successful myotomy. Finally, the mucosal entry site is closed.[47] (Figures 2a-f)

Efficacy

Inoue et al. published the first prospective cohort study in 2010 which showed a significant reduction in symptom score (10 to 1.3; p=0.0003) and LES pressure (52.4mmHg to 19.9mmHg; p=0.0001).[47] Since then, many meta-analyses have demonstrated high clinical success in 90-97% of patients.[48,49,50,51,52] Vespa et al. performed one of the largest meta-analyses of 31 studies with 3,023 patients revealing a clinical success rate of 91% at a median follow-up of 29-months.[53] Zhang et al. analyzed symptom resolution over time and reported clinical success rates of 91.3%, 90.4%, 89.8%, and 82.2% at 2, 3, 4, and 5 years, respectively.[54] Post-POEM quality of life also significantly ($p<0.05$) improved according to a meta-analysis by Zhong et al.[55]

Shou et al. identified risk factors for POEM failure in a meta-analysis of 27 studies with 9,371 patients.[56] Worse outcomes occurred in patients with a sigmoid esophagus (a manifestation of advanced achalasia) (OR 1.90, 95% CI 1.45-2.47), type I achalasia (OR 1.30, 95% CI 1.04-1.63), type III achalasia (OR 1.26, 95% CI 0.89-1.78), prior Heller myotomy (OR 5.75, 95% CI 3.97-8.34), and prior PD (OR 1.18, 95% CI 1.07-1.29).[56] Better outcomes occurred in patients with type II achalasia (OR 0.59, 95% CI 0.47-0.75).[56] In contrast, there was no significant difference in symptom resolution between achalasia subtypes according to meta-analyses by Zhang et al. and Andolfi et al.[54,57] POEM was examined in the elderly patient population by Hayat et al. who found no significant difference in success among patients ≥65-years-old (95.74% vs 95.31%) or ≥75-years-old (99.01% vs 97.97%) compared to their younger counterparts.[58]

When initial POEM fails, repeat POEM may be attempted with good outcomes. Hayat et al. analyzed 6 studies with 123 patients who underwent repeat POEM 12.2-13.5 months on average after their initial failed POEM.[59] 82.69% of patients achieved clinical success after repeat POEM.[59]

To optimize outcomes, many variations in POEM technique have been studied.[60] Dhoop et al. compared full-thickness and circular myotomy and found no significant difference in clinical success at 1 or 3 years.[61] However, full-thickness myotomy had an increased risk for post-POEM GERD (RR 3.03, 95% CI 1.53-6.02; p=0.002) and esophagitis (RR 1.79, 95% CI 1.09-2.76; p=0.02) compared to circular myotomy.[61] Rodriguez de Santiago et al. and Mohan et al. performed meta-analyses comparing anterior and posterior wall tunneling, each finding no significant difference between myotomy approaches.[52,62] Procedure time was shorter with posterior (62.1 minutes) compared to anterior (82.7 minutes) wall tunneling.[62] In practice, individual operators are free to perform POEM as they see fit.

Optimal myotomy length has been extensively studied, comparing short and long myotomy lengths. Zhang et al., Weng et al., and Ghazaleh et al. performed meta-analyses which showed shorter myotomy resulted in shorter procedure times, as expected, with the same or less risk of reflux but no significant difference in clinical success.[63,64,65]

POEM has also been successfully used as rescue therapy following failed improvement with other treatment modalities for achalasia. Tan et al. and Zhong et al. demonstrated clinical success in 90.8% and 91.0% of these patients, respectively.[66,67]

Adverse Events

Symptomatic reflux and reflux esophagitis are two of the most common adverse events seen following POEM with rates ranging from 22.0-26.2% and 5.9-19.0%, respectively.[47,48,49,53,54,68,69] Mota et al. performed a meta-analysis of 25 studies and found no statistical difference in post-POEM GERD rates when comparing full-thickness, partial-thickness and circular myotomy, anterior and posterior myotomy, or subtypes of achalasia.[70] This differs from Dhoop et al.'s more recent meta-analysis which showed an increased risk of post-POEM GERD and esophagitis with full-thickness myotomy.[61] POEM combined with fundoplication (POEM-F) has been trialed in an attempt to reduce post-POEM reflux. The rate of post-POEM-F reflux reported by Gopakumar et al.'s meta-analysis of 7

studies with 127 patients was 13.8% which is lower than most reflux rates after POEM alone but comes with far higher costs.[71]

Serious adverse events include subcutaneous emphysema (21.8-31.6% of patients), pneumoperitoneum (16.2-30.6%), pneumothorax (8.7-11.0%), and in very rare instances, mediastinal emphysema/leak (0.3-4.9%), esophageal/gastric perforation (2.6%), bleeding (0.9-1.1%), and death (0.09%).[48,69]

CONCLUSION

Achalasia is a complex and debilitating esophageal motility disorder, but there are many efficacious endoscopic treatment options available, enabling individualized treatment approaches. Botulinum toxin injections have shown decent short-term clinical success with few adverse events and are best suited for older patients and/or those who are not candidates for more invasive endoscopic modalities. Pneumatic dilation has shown better short-term outcomes but is limited by high rates of symptom relapse and a small risk of serious adverse events, most notably esophageal perforation. Peroral endoscopic myotomy offers the highest long-term success rates but may be accompanied by post-procedural reflux symptoms and/or reflux esophagitis. Treatment should be tailored to patient preferences and institutional expertise. ■

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Answers to this month's crossword puzzle: