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Diagnostic and Management Modalities of achalasia

Ahmed Mohamed Ahmed El-Marakby[1], Sherif Mohamed Galal[1], Nagy Fawzy Mohamed[2], Sameh Mahmoud Abdelmoniem[1],Shaimaa Mohamed Abelmonem Elkholy[3]

1 Tropical Medicine Department, Faculty of Medicine - Zagazig University, Egypt
2 Psychiatry Department, Faculty of Medicine - Zagazig University, Egypt
3 Internal Medicine Department, Faculty of Medicine - Cairo University, Egypt
Corresponding author: Ahmed Mohamed Ahmed El-Marakby
Email: amarakbi24@gmail.com, ahmed.elmarakbi@medicine.zu.edu.eg

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Abstract: Background: Dysphagia is considered an alarm symptom that mandates the performance of esophagogastro-duodenoscopy (EGD) as an initial diagnostic modality to exclude structural or mucosal lesions in the esophagus or the stomach cardia. Examples of these include tumors, inflammation, esophageal rings, strictures, and other pathologies that can mimic achalasia, a condition traditionally named pseudochalasia. Classic endoscopic findings of achalasia present in about half of the cases include widening of the esophagus, residue in the esophageal lumen, and obstructed EGJ. An additional important diagnosis is eosinophilic esophagitis (EoE), an immune-mediated/allergic disorder involving the esophagus causing dysphagia and diagnosed by eosinophils predominant inflammation. The diagnosis of achalasia is supported by esophagram findings including dilation of the esophagus, a narrow EGJ with " birdbeak " appearance, aperistalsis, and poor emptying of barium. It may also be helpful in cases where esophageal manometry may be associated with equivocal findings

Keywords: *Diagnostic, Management Modalities of achalasia*

Introduction

High-resolution esophageal pressure topography (HREPT) studies demonstrated a population of patients with impaired LES relaxation with remaining peristaltic of the tubular esophagus that fails to meet diagnostic criteria of achalasia, similar to those with 'atypical disorders of LES relaxation' in conventional manometry [1,2]. This disorder was called functional obstruction in the first Chicago classification schemes. Further on, it could be demonstrated that these patients had an elevated intrabolus pressure, similar to patients with a known mechanical obstruction, and therefore it is now categorized as EGJ outflow obstruction [3]. However, because the primary dysfunction in EGJ outflow obstruction and achalasia is failure of swallow-induced LES relaxation, symptoms and treatment are often similar. It has been reported to occur in benign and malignant infiltrative disorders or may be a variant or earlier form of achalasia [2].

Diagnosis of achalasia

• Diagnostic Approach to Dysphagia and Achalasia

Dysphagia is considered an alarm symptom that mandates the performance of esophagogastro-duodenoscopy (EGD) as an initial diagnostic modality to exclude structural or mucosal lesions in the esophagus or the stomach cardia. Examples of these include tumors, inflammation, esophageal rings, strictures, and other pathologies that can mimic achalasia, a condition traditionally named pseudochalasia [4,5]. A clinical suspicion of pseudo-achalasia should be sought in patients older than 55 years of age with a prompt onset of solid dysphagia that proceeds to liquid dysphagia and weight loss [4,5].

Classic endoscopic findings of achalasia present in about half of the cases include widening of the esophagus, residue in the esophageal lumen, and obstructed EGJ. An additional important diagnosis is eosinophilic esophagitis (EoE), an immune-mediated/allergic disorder involving the esophagus causing dysphagia and diagnosed by eosinophils predominant inflammation [4,5]. Multiple biopsies are mandatory to confirm the diagnosis. Indicative endoscopic findings of EoE include mucosal thickening and edema, ring formation, and white patchy exudates and fibrosis in the late stage. After the exclusion of anatomical, structural, and inflammatory conditions, HRM study is necessary to assess the esophageal motor function and the relaxation of the lower sphincter [4,5].

Symptomatology

The most frequently occurring symptoms of achalasia are dysphagia (>90%) for solids and liquids, regurgitation of undigested food (76–91%), respiratory complications (nocturnal cough [30%] and aspiration [8%]), chest pain (25–64%), heartburn (18–52%), and weight loss (35–91%) [6]. Heartburn can lead to an erroneous diagnosis of gastro- oesophageal reflux disease, which might culminate in antireflux surgery. Nocturnal coughing mainly occurs in patients with substantial stasis of large amounts of food and secretions. Chest pain is predominantly present in patients with type III disease) and responds less well to treatment than do dysphagia and regurgitation, which probably explains the less favorable therapeutic results obtained in patients with type III disease compared with those with type I or II disease [7].

However, symptoms of achalasia are not specific, which explains the long delay between onset of symptoms and the final diagnosis (up to 5 years in some studies). Although some patients lose a lot of weight (more than 20 kg), achalasia should also be considered in obese patients [7].

1- Contrast studies

The diagnosis of achalasia is supported by esophagram findings including dilation of the esophagus, a narrow EGJ with " birdbeak " appearance, aperistalsis, and poor emptying of barium. It may also be helpful in cases where esophageal manometry may be associated with equivocal findings [8]. In addition to supporting the diagnosis of achalasia, an esophagram is also useful to assess for late- or end-stage achalasia changes (tortuosity, angulation, megaesophagus) that have implications for treatment. An additional role for radiological examination is to provide objective assessment of esophageal emptying after therapy. In many patients with achalasia, symptom relief does not always parallel esophageal emptying [9]. This was initially demonstrated by measuring barium column height 1 and 5 min after upright ingestion of a large barium bolus; an approach that has come to be known as the " timed barium esophagram " (TBE) [10]. Subsequent data suggested usefulness of TBE for the objective evaluation of achalasia patients after treatment, as it helps identify patients who are more likely to fail treatment despite initial symptomatic improvement [11].

2- Upper digestive endoscopy

Endoscopy may suggest the diagnosis of achalasia but has low accuracy. The esophageal body may appear dilated, atonic, and often tortuous at endoscopy in more advanced degrees of achalasia. Some resistance to pass the cardia may be noticed. Esophageal mucosa may be normal but esophagitis with friability, thickening, and even erosions may be noticed secondary mainly to chronic stasis [12]. Upper endoscopy must be performed in all patients with dysphagia and suspected achalasia. The main reason is to rule out esophageal cancer, or the development of premalignant or malignant lesions secondary to chronic stasis [13]. Pseudoachalasia results from tumors at the esophagogastric junction and mimic classic achalasia, although clinical differences, such as older patients, greater weight loss and shorter duration of symptoms are seen. These tumors may be missed

endoscopically in up to 60% of patients with pseudoachalasia due to a submucosal presentation [8]. Endoscopic ultrasonography and CT scan may prove useful in patients with non-diagnostic endoscopy, and high degree of clinical suspicion for pseudoachalasia, but it are not recommended as a routine tests in achalasia. Achalasia is an important risk factor for esophageal cancer with an incidence of up to 9% of cancer developing in achalasia or 10-50 times higher than the general population [12].

3- Esophageal manometry:

The procedural basis for both types of manometry, i.e. CM or HRM, is the same. Both begin with placement of the manometry catheter transnasally until the distal pressure sensors cross the esophagogastric junction (EGJ) and enter the stomach. Patients are instructed to fast overnight and to omit any medications that might affect motility for 48 h prior to the manometry [2].

 Conventional manometry [1]

CM can be performed with the use of a low-compliance capillary perfusion system or a solid state assembly with pressure sensors, usually spaced at 3-5 cm intervals. A stationary pull-through method is used to determine the position of the LES and to identify the pressure inversion point and a high-pressure zone. The LES resting pressure and relaxation in response to 5 wet swallows is measured with the pressure sensor in the middle of the LES high pressure zone [14]. Esophageal body motility is assessed by repositioning the pressure sensors into the body. The response to 10 wet swallows separated by an interval of at least 30 sec is tested. The diagnosis of classic achalasia is characterized by complete absence of peristalsis in the body of the esophagus (simultaneous contractions with amplitudes <40 mmHg or no apparent esophageal contraction) and incomplete relaxation of a hypertonic or normotonic LES. Atypical presentations of achalasia have been described by conventional manometry. These include cases with preserved peristalsis and/or esophageal contractions with amplitudes greater than 40 mmHg, the latter situation often being referred to as “vigorous achalasia” [15].

 HRM [2]

An HRM device is composed of multiple, closely spaced pressure sensors (usually 1 cm apart). HRM provides much more information than CM, as data are not lost in the 3-5 cm sized gaps between the sensors of CM. In contrast to the station pull-through method of the CM, the HR- assembly needs no further repositioning once it has been placed across the EGJ [2]. This makes the procedure much more comfortable for the patients. Advantages of HRM over CM is the simultaneous assessment of the upper and LES as well as the esophageal body peristalsis with a single series of swallows, which makes the data acquisition period shorter than with CM. However, the main innovation of this method is the conversion of pressure data into a topographical plot. The data can be modified using interpolation to generate HREPT plots that are color-coded, spatiotemporal representations of pressure recordings in the esophagus (Clouse Plots). Colors are assigned to the pressures with cool colors (blue and green) for lower pressures and warm colors (red and yellow) for high pressures [16].

Analysis of a HREPT study is performed by using a stepwise approach focused on an algorithm-based scheme that first assesses EGJ relaxation pressures and subsequently uses individual swallow patterns defined by HREPT metrics to further subclassify the patient into specific categories [2].

 Specific achalasia subtypes

The classification of achalasia has evolved with the introduction of HREPT. Different achalasia subtypes have been described, all of which are associated with abnormal EGJ relaxation and are categorized based on the pattern of esophageal body contraction and pressurization (Table 1,Figure1). [17]

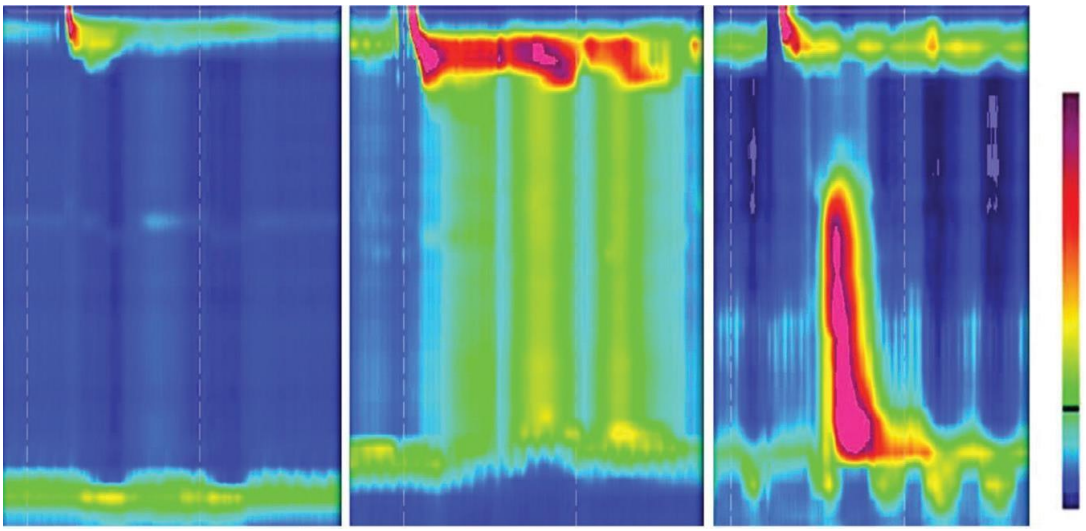

Figure 1: High-resolution esophageal pressure topography showing the 3 different types of achalasia [2].

Table 1: Manometric variants of achalasia [2].

Type I 100% failed peristalsis (minimal pressurization within the esophagus)
Type II No normal peristalsis, panesophageal pressurization (>30 mmHg in ≥10% of wet swallows)
Type III Spastic achalasia (no normal peristalsis, preserved fragments of distal peristalsis or premature contractions in ≥20% of swallows)

Thus, by HREPT, achalasia can be subtyped into classic achalasia (with no esophageal pressurization by swallowing), achalasia with esophageal pressurization (characterized by compression of the water bolus between the upper and LES), and spastic achalasia (characterized by nonpropulsive, high-amplitude contractions in the esophageal body) [2].

4- EndoFLIP

Endoflip is a novel diagnostic device that permits measurement of the level of distensibility at the esophagogastric junction as well as is capable of detecting the various achalasia subtypes with a high level of confidence and accuracy, particularly with the advent of combining distensibility sensors to manometry sensors. The test is performed while the patient is sedated, eliminating the inconvenience related to HRM and potentially replacing it in select patients [4].

5- Ambulatory 24-Hour pH Monitoring

This test is recommended in selected patients when the diagnosis is uncertain, to distinguish between GERD and achalasia. The study is performed after discontinuing acid-suppression medications 10 days (proton pump inhibitors) or three days (histamine-2 receptor antagonists) before the study. The dual-channel pH catheter with two sensors located 15 cm apart is placed transnasally so that the distal and the proximal sensors are positioned 5 and 20 cm above the upper border of the manometrically determined LES [4]. Gastroesophageal reflux is evaluated in terms of the number of reflux episodes and amount of acid exposure (pH < 4). The examination of the pH-monitoring tracing is mandatory. In both GERD and achalasia, the test can be abnormal, but the tracing is different. Although in GERD patients the tracing is characterized by intermittent drops of pH below 4 with subsequent return of the pH values above 5, in achalasia patients there is a slow and progressive drift of the pH below 4 with no return to higher values (pseudo-GERD due to food fermentation) [6].

Treatment of achalasia

• Pharmacologic therapy

Oral pharmacologic therapies are the least effective treatment options in achalasia. Calcium channel blockers and long-acting nitrates are the two most common medications used to treat achalasia. They transiently reduce LES pressure by smooth muscle relaxation, facilitating esophageal emptying. The phosphodiesterase-5-inhibitor, sildenafil, has also been shown to lower the LES tone and residual pressure in patients with achalasia [18]. Other less commonly used medications include anticholinergics (atropine, dicyclomine, cimetropium bromide), β -adrenergic agonists (terbutaline), and theophylline. Overall, calcium channel blockers decrease LES pressure by 13 – 49 % and improve patient symptoms by 0 – 75 %. The most commonly employed calcium channel blocker is nifedipine, showing time to maximum effect after ingestion of 20 – 45 min with duration of effect ranging from 30 to 120 min [19]. Thus, it should be used (10 – 30 mg) sublingually 30 – 45 min before meals for best response. Sublingual isosorbide dinitrate is also effective in decreasing LES pressure by 30 – 65 %, resulting in symptomatic improvement ranging from 53 to 87 %. It has a shorter time to maximum reduction in LES pressure (3 – 27 min) than sublingual nifedipine but also has a shorter duration of effect (30 – 90 min) [20]. Hence, sublingual isosorbide dinitrate (5 mg) is commonly administered only 10 – 15 min before meals. The only comparative study of sublingual nifedipine to sublingual isosorbide dinitrate showed a nonsignificant edge in LES pressure reduction with the latter (65 %) than the former (49 %) [21].

The clinical response with pharmacologic agents is short acting and the side effects, such as headache, hypotension, and pedal edema, are common limiting factors in their use. Furthermore, they do not provide complete relief of symptoms. Thus, these agents are commonly reserved for patients with achalasia who cannot or refuse to undergo more definitive therapies (PD or surgical myotomy) and those who have failed botulinum toxin injections [22].

• Endoscopic Botolium Toxin Injection

Toxin botulinum is a neuro toxin works to inhibit neurotransmitter in terminal cholinergic receptor. Botulinum toxin-A that used for Achalasia therapy works by breaks SNAP-25 protein molecule in presynaptic membrane, so that acethylcholine release was blocked and inhibit acetylcholine exocytosis to synaptic area. This will result in transient muscle weakness by blocking cholinergic stimulation in LES (Figure 2) [1].

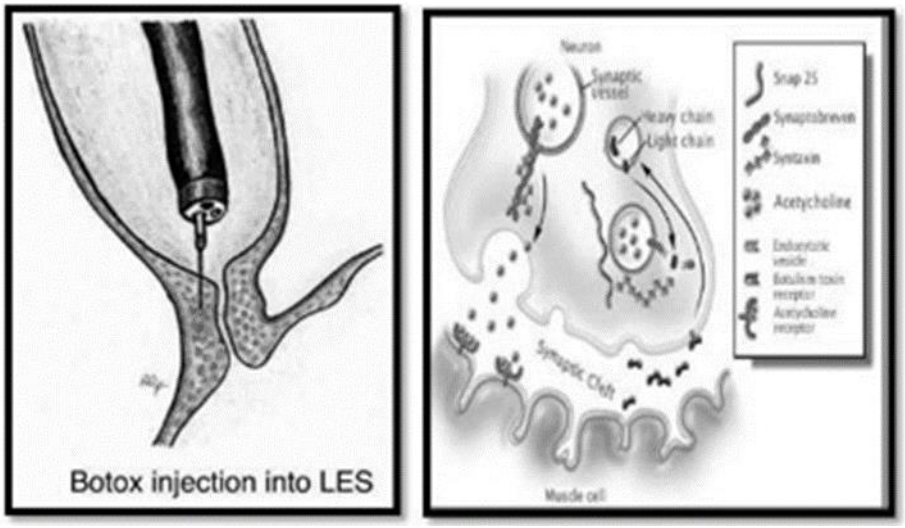

Figure 2: Botulinum toxin mechanism of action and injection location [23].

Botulinum toxin injection locally could reduce LES pressure and increase esophagus passive emptying. Toxin injected via sclerotherapy during endoscopy. In normal condition, 80 to 100 unit of Botulinum toxin- A was injected in each LES quadrant to reduce its pressure, increase esophageal opening, and improve esophageal emptying [23]. The clinical effect from single injection was short term effect with relapse incidence more than 50% in 6 months. Otherwise, repeated injections could give more effect in 70-90% patients. A report showed

that 21% of newly diagnosed Achalasia patients was treated using botulinum toxin as early modalities with injection duration of 6 months. Good response from botulinum toxin injection was found in patients aged less than 50 years old and patients with severe Achalasia [24].

This therapy was safe, only 10% complained chest pain after injection but mostly did not require specific therapy. But repeated injection could make myotomy procedure during surgery seems harder because of adhesion of muscular layer and increase perforation possibility in mucosa. Regarding to patient safety, botulinum toxin injection could be given if no other choice present or if surgery correction contraindicated, and in patients with survival rate of 2 years (expected short- term expectancy) [23].

• Pneumatic dilatation

Pneumatic dilatation, which tears the LOS by forceful stretching with air-filled balloons, has become simplified by the microinvasive Rigiflex balloon system (Boston Scientific, Marlborough, MA, USA). These noncompliant polyethylene balloons are available in three diameters (30, 35, and 40 mm), mounted on a flexible catheter placed over a guide wire at endoscopy [25]. Under fluoroscopic guidance, the balloon is positioned across the LOS and gradually inflated until the waist is flattened. The most popular technique is a graded dilation protocol starting with a 30 mm balloon. Subsequent dilations are spaced over 2–4-week intervals on the basis of symptom relief associated with repeat LOS pressure measurements or improvement in oesophageal emptying [26].

Pneumatic dilatation is usually done in an outpatient setting; the patient is observed for 2–6 h and can return to normal activities the next day. In a review of more than 1100 patients (24 studies) with an average follow-up of 37 months, Rigiflex pneumatic dilatation resulted in good to excellent symptom relief in 74%, 86%, and 90% of patients treated with 30, 35, and 40 mm balloons, respectively [27]. Over 4–6 years, nearly a third of patients have symptom relapse; however, long-term remission can be achieved in nearly all these patients by repeat dilatation by an on-demand strategy on the basis of symptom recurrence66. Patients with the best outcomes after pneumatic dilatation are those older than 40 years, women, and those with a type II pattern by HRM [27].

Contraindications to pneumatic dilatation are poor cardiopulmonary status or other comorbid illnesses that would prevent surgery should an oesophageal perforation occur. Pneumatic dilatation can be done safely after a failed Heller myotomy, although larger diameter balloons are often needed [28]. Up to 33% of patients have procedure related complications after pneumatic dilatation, but most are minor including chest pain, aspiration pneumonia, bleeding, transient fever, mucosal tear without perforation, and oesophageal haematoma. Oesophageal perforation is the most serious complication, with an overall rate in experienced endoscopists of 2·0% (range 0–16%), of which 50% needed surgery [29]. However, in a recent series of 16 transmural perforations, all cases were managed conservatively. Small perforations and painful deep tears can be treated with antibiotics and total parenteral nutrition for days to weeks [6]. However, surgical repair by thoracotomy is best for large, symptomatic perforations with extensive soilage of the mediastinum. Most perforations occur during the initial dilatation; difficulty keeping the balloon in position is a potential risk factor [30]. Although no other predictors for perforation have been identified, a European achalasia trial reported more perforations, primarily in older patients, when the first pneumatic dilatation was done with a 35 mm compared with a 30 mm balloon. Complications of severe gastrooesophageal reflux disease are rare after pneumatic dilatation, but 15–35% of patients have heartburn, which improves with proton-pump inhibitors [6].

• A self-expanding metallic stent (SEMS):

SEMS have been recently proposed as a potential therapeutic strategy for achalasia. They are typically removed 5–6 days after deployment. Experience with SEMS is predominantly limited to several Chinese groups, with only three case series totaling 26 patients reported from European investigators [19]. Overall, technical success as defined by adequate stent deployment and immediate symptomatic control was achieved in all patients. Clinical remission at three years post-intervention ranged from 49–85%, with one prospective non-randomized study reporting a durable long-term remission rate of 83% at ten years [30]. A study also

compared SEMS with pneumatic balloon dilatation and found that SEMS had superior long-term dysphagic control (SEMS 78% vs. pneumatic balloon dilatation 17%) [31].

Despite these encouraging results, patients who received SEMS experienced significantly higher complications than those who underwent pneumatic balloon dilatation or botox injection62. These included bleeding 12%, chest pain 25–40%, gastro-esophageal reflux 20% and stent migration 5–10%, including one case of colonic obstruction by SEMS migration [32].

• Myotomy

The primary surgical goal in the treatment of achalasia is a myotomy of the circular muscle fibers of the LES to create a long-lasting decrease in residual LES pressure. The 2 accepted strategies are LHM with a possible concurrent fundoplication and POEM. Both methods are very effective and should be considered with PD as first-line therapies in appropriate surgical candidates. All therapies, including POEM, should only be done in medical centers with providers who have experience performing the procedures and managing potential complications [33].

• Heller's myotomy

This procedure was initially performed via an open trans-thoracic or trans-hiatal approach with advances in minimally invasive technology over the last 30 years, most surgeons have elected to myotomize the esophagus via a laparoscopic trans-hiatal route [34]. Overall, this technique has excellent efficacy with a technical success rate, as defined by a decrease in symptoms score within the first three months post laparoscopic Hellers myotomy, ranging from 80–100% in contemporary series. This is associated with a mean LES pressure reduction of 40–80% [35]. Prospective trials have reported a five-year recurrence rate post laparoscopic Heller's myotomy of approximately 5–15%Retrospective studies have demonstrated durable disease control from laparoscopic Heller's myotomy with 20–30% of patients experiencing clinical relapse [36]. The failure to alleviate dysphagia is partly attributed to inadequate myotomy length. The learning curve for laparoscopic Heller's myotomy is relatively short and is estimated to be 16–20 cases [37].

Causes of postoperative complications include mucosal perforation, splenic injury, pneumothorax and wound bleeding. GERD is the most common long-term adverse outcome following laparoscopic Heller's myotomy and its incidence increases with time [38]. In those who have undergone a concurrent fundoplication, 7–15% of patients have abnormal acid exposure on pH monitoring. This is associated with a 5–11% risk of erosive esophagitis, and 2–7% risk of symptomatic reflux [38]. Importantly, in comparison to pneumatic balloon dilatation and POEM, laparoscopic Heller's myotomy with fundoplication has the lowest rate of post-interventional GERD. The factors that predict therapeutic success post-LHM include: age >40 years, pre-treatment LES pressures >30 mmHg, and post-treatment LES pressures 50% decrease in LES pressures [39]. Conversely, the factors that predict treatment failure include male gender, daily chest pain, severe preoperative dysphagia, sigmoid esophagus, and type 3 achalasia [39].

• Peroral endoscopic myotomy:

POEM was first introduced by Ortega JA in 1980. In his initial report, seventeen patients with achalasia were treated by endoscopic myotomy limited to esophageal rosette. In this cohort improvement of symptoms and manometry follow-up was comparable to Heller myotomy. The current form of POEM was developed by Inoue in 2008. He utilized a submucosal tunnel to reach the inner circular muscle bundle of the LES to perform the myotomy [40]. Following the initial publication, Inoue et al. presented their experience in performing POEM on 43 patients for the treatment of achalasia. The authors achieved a comparable outcome to Heller's myotomy [41].

POEM is emerging as the treatment of choice for achalasia and is even utilized for prior failed achalasia treatment including laparoscopic surgical myotomy . POEM is also applied to treat other motility disorders including spastic esophageal disorders (SED), such as diffuse esophageal spasm, jackhammer esophagus, or type 3 achalasia [42].

Pre-operative evaluation

In the pre-operative evaluation of achalasia, barium swallow, esophageal manometry and EGD should be performed to confirm diagnosis and exclude other conditions (e.g., cancer). High resolution manometry allows tailored treatment based on the type of achalasia. Patient should be on a clear liquid diet for 2 days before the procedure and NPO the night of the procedure [40]. In some centers, EGD is performed before general anesthesia to remove food remnants and assess for candida esophagitis; another approach is to place a nasogastric tube for suction 1 to 2 days prior to the procedure. Oral antifungal treatment can be administered one week prior to the procedure if candidiasis is suspected. A broad-spectrum antibiotic is usually given intravenously on the day of the procedure. Anticoagulants and anti-platelet medication should be withheld prior to the intervention [43].

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