Management of the patient with esophagogastric junction outflow obstruction

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Purpose of review
Esophagogastric junction outflow obstruction (EGJOO), defined as elevated integrated residual pressure (IRP) with preservation of esophageal peristalsis, is a common finding on high-resolution esophageal manometry.

Recent findings
The recent Chicago classification version 4.0 proposes changes to the criteria for diagnosing EGJOO, making this diagnosis more restrictive to now include elevated IRP in both supine and upright positions (with preservation of esophageal peristalsis), presence of obstructive symptoms, and confirmatory tests for EGJOO, such as timed barium esophagram with barium tablet or functional lumen imaging probe.

Summary
Once the diagnosis of EGJOO is established, secondary causes need to be ruled out, especially the use of opioid medications. Upper endoscopy is needed for evaluation of EGJOO patients, though cross-sectional imaging is usually not necessary. Many patients improve without intervention; thus, expectant management is recommended for patients with mild or atypical symptoms. There seems to be a limited role for medical treatment. Botox injection into the lower esophageal sphincter is often used to see if the patient improves before committing to more definitive treatments, such as pneumatic dilation, peroral endoscopic myotomy, or Heller myotomy.

Keywords
dysphagia, EGJOO, high-resolution esophageal manometry, outflow obstruction

INTRODUCTION

Esophagogastric junction outflow obstruction (EGJOO) is a manometric finding that has been described with esophageal high-resolution manometry (HRM) [1▪▪]. Chicago Classification version 3.0 defined EGJOO as impaired relaxation of the esophagogastric junction (EGJ) manifested by elevated integrated relaxation pressure (IRP) on HRM, with preserved esophageal peristalsis (see Fig. 1) [2]. Although EGJOO is a common finding, the exact clinical significance, impact on symptomatology and quality of life, natural disease course, and best treatment modalities are still not well understood [1▪▪]. This manuscript discusses these areas regarding EGJOO.

DESCRIPTION OF ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

EGJOO can be divided into two groups: primary (also known as idiopathic, functional, or achalasia type IV) and secondary [3▪▪]. Secondary forms include EGJOO caused by mechanical EGJ obstructions, such as masses, strictures, hiatal hernia, vascular compressions, esophageal rings, and diverticula. Other forms of secondary EGJOO include postsurgical (e.g., Nissen fundoplication, gastric banding), infiltrative diseases (e.g., eosinophilic esophagitis (EoE), amyloidosis), and medication-related, most prominently opioids [3▪▪]. In the absence of large population studies, the true prevalence of EGJOO is not known, but tertiary care centers report a prevalence of EGJOO in 3–21% of patients referred for HRM, with an average age of 56–67 years, 51–88% females, and body mass index of 25–30 [1▪▪]. Primary EGJOO is reported in 34–92% of all EGJOO patients; however, EGJOO in a significant portion these patients would now be considered artifactual as the impaired

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KEY POINTS

- Chicago classification version 4.0 has addressed the concern of overdiagnosis of EGJOO by adding more stringent criteria including the need for obstructive symptoms and for confirmation with tests other than manometry (timed barium esophagram along with barium tablet, functional lumen imaging probe) for a definitive diagnosis.
- Once the diagnosis of EGJOO is established, secondary causes need to be evaluated, especially the use of opiate pain medications.
- Many patients improve without intervention and an observant watchful waiting approach is recommended for patients with mild or atypical symptoms.
- Treatments are aimed at disrupting the LES and include botulinum toxin injection, pneumatic dilation, and esophagomyotomy (peroral endoscopic myotomy or Heller myotomy).
- Large-scaled randomized trials are needed to determine the optimal treatment approach for patients with EGJOO.

EGJ relaxation is not seen in the upright position [1▪▪]. Figure 1 shows examples of normal swallow, achalasia (types I, II, III), and EGJOO.

Several studies have demonstrated that EGJOO can be associated with opioid use [1▪▪]. In a retrospective study of 121 chronic opioid users who underwent HRM, 66 patients (45%) stopped opioids for at least 24 h prior to the procedure, and EGJOO was less prevalent in those patients than in the patients who did not stop opioids [4]. Another study of 56 EGJOO patients, 40 patients with hypercontractile esophagus, and 33 controls showed a higher prevalence of opioid use and anticholinergic medication use among the EGJOO and hypercontractile esophagus groups [5]. Several nonopioid medications have been reported to be associated with EGJOO, including anticholinergics, inhaled beta-antagonists, anticonvulsants, tricyclic antidepressants (TCA), benzodiazepines, and serotonin/norepinephrine reuptake inhibitors [6].

The most common presenting symptom in patients with EGJOO is dysphagia, followed by chest pain, regurgitation, and heartburn. EGJOO also can be asymptomatic and found incidentally during HRM performed for indications other than dysphagia, such as preoperative evaluation for antireflux surgery or lung transplant [3▪▪,7]. One study found that dysphagia was the most common symptom (68%), but 5% of patients with EGJOO had no symptoms [8].

The natural course of EGJOO is unpredictable and variable, ranging from spontaneous resolution to progression to achalasia [1▪▪]. Triadafilopoulos *et al*. repeated HRM in ten EGJOO patients, and only five had EGJOO on the second HRM, whereas two had distal esophageal spasm (DES), and three had ineffective esophageal motility (IEM). They also showed concomitant motility disorders with EGJOO on initial HRM, such as IEM, DES, or hypercontractile esophagus, and all groups had a higher percentage of incomplete bolus clearance [9]. Spontaneous resolution has been observed in 15–74% of patients within 6 months [3▪▪]. The evolution of EGJOO to achalasia appears to be rare.

DIAGNOSIS

The diagnosis of EGJOO is based on HRM. The second iteration of the Chicago classification in 2012 defined EGJOO as an elevated mean IRP (with a cutoff value of 15 mmHg) with preserved peristalsis. Chicago classification version 3.0 in 2015 suggested using the median IRP instead, as the mean value could be unduly influenced by outliers [2]. We have observed that some centers still use the old criteria (mean IRP) in their diagnosis and clinical decision making. Furthermore, it is worth noting that the 15 mmHg upper limit of IRP is based on using the Sierra Scientific (now Medtronic, Given) catheters, and other equipment may have different values for the upper limit of normal IRP. The 15 mmHg cutoff value was based on a study of 400 patients and 75 controls, and 15 mmHg was the 95th percentile for a 4 s postswallow segment of EGJ relaxation, with a sensitivity of 98% and specificity of 96% for detecting achalasia [10]. This could mean that up to 5% of normal subjects could be classified as having EGJOO [1▪▪].

In light of these limitations, the recently introduced Chicago classification version 4.0 requires other manometric and nonmanometric evaluations to arrive at a conclusive and actionable diagnosis of EGJOO [11▪]. According to this Chicago classification iteration, three conditions need to be met for a diagnosis of EGJOO: (1) HRM findings: elevated median IRP in both supine and upright positions as well as at least 20% of swallows exhibiting intrabolus pressurization (after excluding achalasia); (2) obstructive esophageal symptoms of dysphagia and/or noncardiac chest pain; (3) confirmatory findings on non-HRM tests such as timed barium esophagram (TBE) also with a barium tablet, or functional lumen imaging probe (FLIP).

Using both supine and upright positions for diagnosis of EGJOO was supported by a large study of 1911 patients at Northwestern University who had HRM, of whom 16.2% had EGJOO, and 16% of those EGJOO patients had normalized IRP (defined

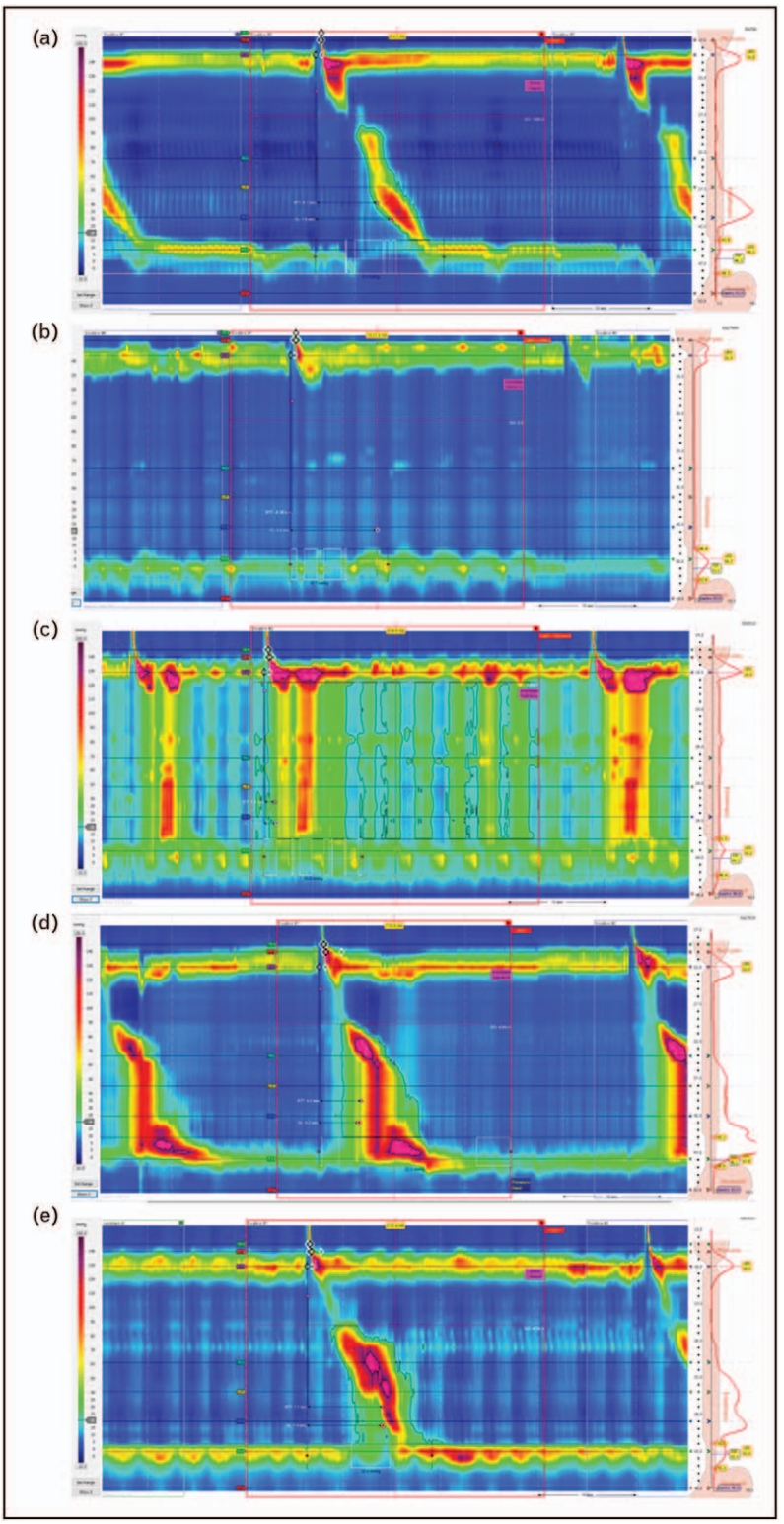

FIGURE 1. HREM findings of (a) normal swallow, (b) type 1 achalasia, (c) type 2 achalasia, (d) type 3 achalasia, (e) EGJOO swallow with elevated IRP and high intrabolus pressure.

as < 12 mmHg) when HRM was performed in the upright position [12]. Figure 2 shows examples of supine and upright swallows in patients with elevated supine IRP.

Provocative testing including rapid drink challenge (RDC) and solid foods during HRM has been shown to increase the diagnostic yield of clinically significant EGJOO. In a recent retrospective study of

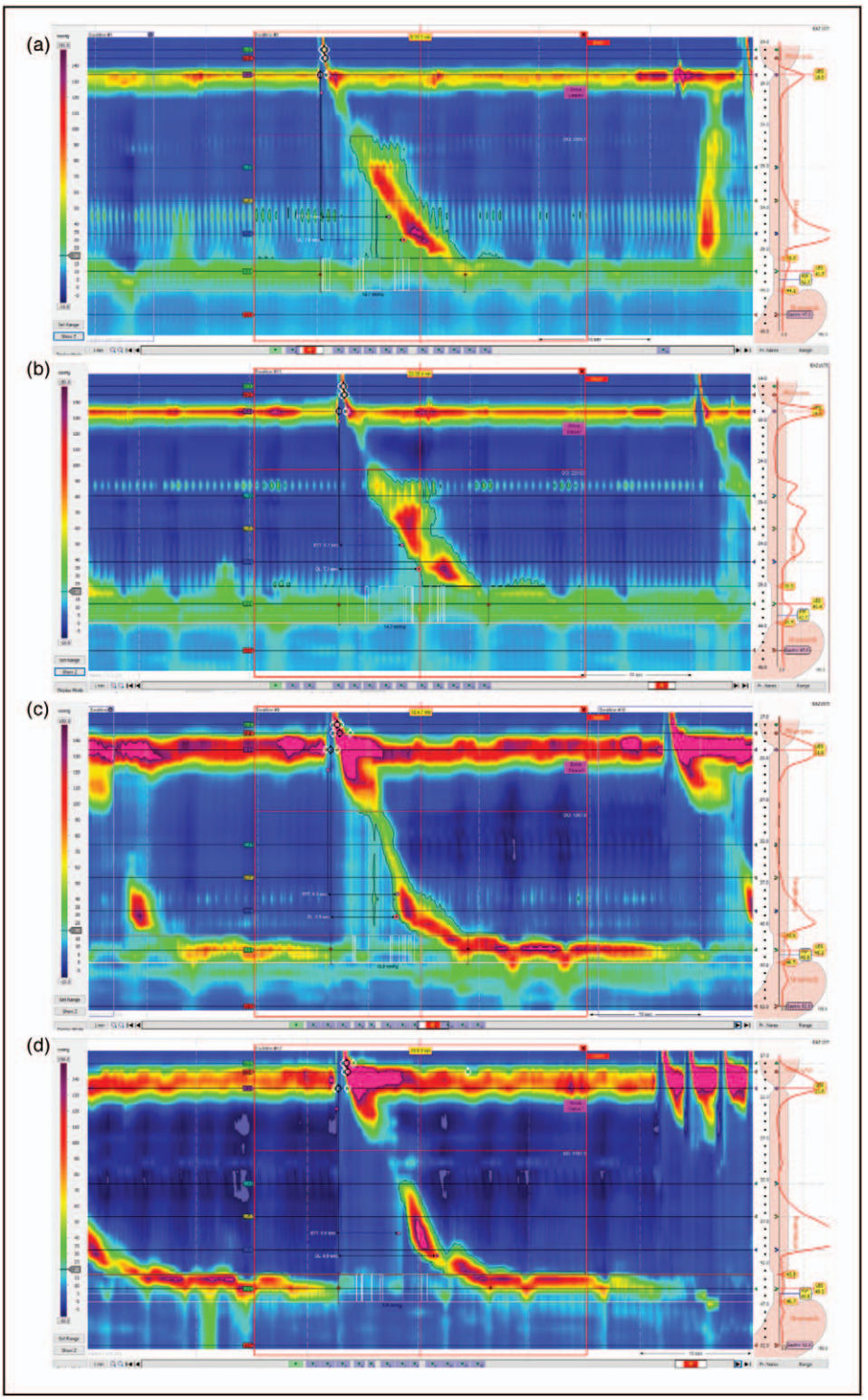

FIGURE 2. Examples of supine and upright swallows to assess for EGJOO in patient with elevated supine IRP. A patient with elevated IRP both in the supine and upright positions is shown in (a) and (b). This patient meets partial criteria for EGJOO. A subject with elevated IRP supine but normal IRP in the upright position is shown in (c) and (d). This patient does not meet the manometric criteria for EGJOO by Chicago Classification 4.0.

121 EGJOO patients (25% confirmed with TBE and 84% identified as primary EGJOO), symptom-positive EGJOO patients were more likely to show abnormal motility or esophageal pressurization during RDC but not with traditional 5 ml water swallows [13]. Furthermore, RDC showed higher sensitivity in identifying treatment responders (85%) compared to traditional single swallow and TBE. In another study of 101 patients with EGJOO identified on HRM based on Chicago classification 3.0, 32% had radiographic EGJOO (defined as either liquid barium retention on TBE at 1 min or delayed passage of a 12.5 mm barium tablet), and these patients (compared to controls and those without radiographic EGJOO) showed more frequent IRP elevation in the upright position (> 12 mmHg), during RDC, and multiple rapid swallows (MRS) [14▪]. Figure 3 shows examples of single swallow and MRS

Barium esophagrams may be useful in assessing clinically important EGJOO by demonstrating esophageal retention of barium above the EGJ (Fig. 4). Studies by our group showed that videoesophagography is very helpful in evaluating patients with dysphagia symptoms, primarily in detecting the major esophageal motility disorders, but with 50% positive predictive accuracy for isolated lower esophageal sphincter (LES) dysfunction. In another study, esophagrams were performed in 40 patients with EGJOO on HRM, and the diagnostic yield of esophagrams was 73%, with hiatal hernia detected in 50%, dysmotility in 43%, and EGJ narrowing seen in 25% of patients [15].

TBE with liquid barium followed by a barium tablet can also provide complimentary information about anatomy and motility. For the timed barium esophagram, the patient drinks 8 oz of low-density barium in the standing position, followed by spot upright films at 1 and 5 min to assess liquid esophageal emptying. TBE for liquid barium is considered normal if barium height is less than 5 cm in the distal esophagus at 5 min [16]. Often the TBE is followed by rinsing the esophagus with water followed by ingestion of a 13 mm barium tablet. Tablet passage is evaluated after 5 min with an abnormal test being tablet retention in the esophagus.

TBE is used primarily in the assessment of achalasia. Blonski *et al.* in a retrospective study of 309 patients demonstrated that a barium height of ≥ 5 cm at 1 min and ≥2 cm at 5 min was able to differentiate untreated achalasia from nonachalasia disorders (including EGJOO) [16]. A barium height of 6 cm at 1 min showed good accuracy in differentiating achalasia from EGJOO with a sensitivity of 91% and specificity of 56%. A barium column height of 2 cm at 5 min showed good accuracy in differentiating achalasia from EGJOO with a sensitivity and specificity of 84%. In contrast, the TBE does not reliably distinguish EGJOO from nonachalasia causes of dysphagia. A barium height of 4 cm at 1 min showed poor accuracy in differentiating EGJOO from nonachalasia disorders with a sensitivity of 50% and specificity of 73%. However, the combination of liquid barium and barium tablet retention increased the diagnostic yield in EGJOO patients from 48.9% (only barium tablet lodged) to 60%. In a treatment study of pneumatic dilation for patients with idiopathic EGJOO, criteria for EGJOO on TBE included >4 cm of retained liquid barium in the esophagus at 1 min and/or pill arrest in esophagus at 5 min. This cutoff was based on the above findings of Blonski *et al.* whose study revealed that a 4 cm retained barium column at 1 min distinguishes idiopathic EGJOO from nonachalasia patients.

FLIP technology is increasingly being used to assess EGJ diameter and distensibility, and the esophageal body response to FLIP balloon distention. FLIP uses high-resolution impedance planimetry to measure the relationship of luminal dimensions and distensibility during volumetric distention (Fig. 5) [17]. It has shown utility in assessing physiology and treatment response in achalasia, EoE, gastroesophageal reflux disease, systemic sclerosis, and IEM [3▪▪]. Carlson *et al.* in a study of 145 patients, including 38 with EGJOO, demonstrated an abnormal EGJ distensibility index in patients with achalasia and EGJOO compared to IEM and patients with normal motility [17]. They proposed a protocol to approach esophageal dysmotility using FLIP topography which involves distension of the FLIP balloon and observing the reaction of the esophageal body. EGJOO is diagnosed if EGJ distensibility is low (<2.0 mm^2/mmHg) but normal antegrade contractions are present after balloon distension. In this study, 95% of patients who had abnormal HRM also had abnormal FLIP topography (including all patients with achalasia), but 50% of patients with normal HRM had abnormal FLIP findings (including IEM and EGJOO). One drawback is that FLIP technology is not widely available and further studies are needed to confirm the clinical utility of FLIP topography [1▪▪].

FLIP panometry has also been suggested to help select management strategies for patients with EGJOO: patients with a low EGJ-distensibility index responded well to achalasia-type treatment, whereas patients with normal EGJ-distensibility index had good outcomes from conservative management [18]. In this study of FLIP panometry in 34 patients with idiopathic EGJOO on HRM, only seven (21%) had a normal EGJ-distensibility index, and all had repetitive antegrade contractions. None of these patients had radiographic evidence of EGJOO, defined as liquid barium retention and/or barium tablet retention. All 18 patients with radiographic

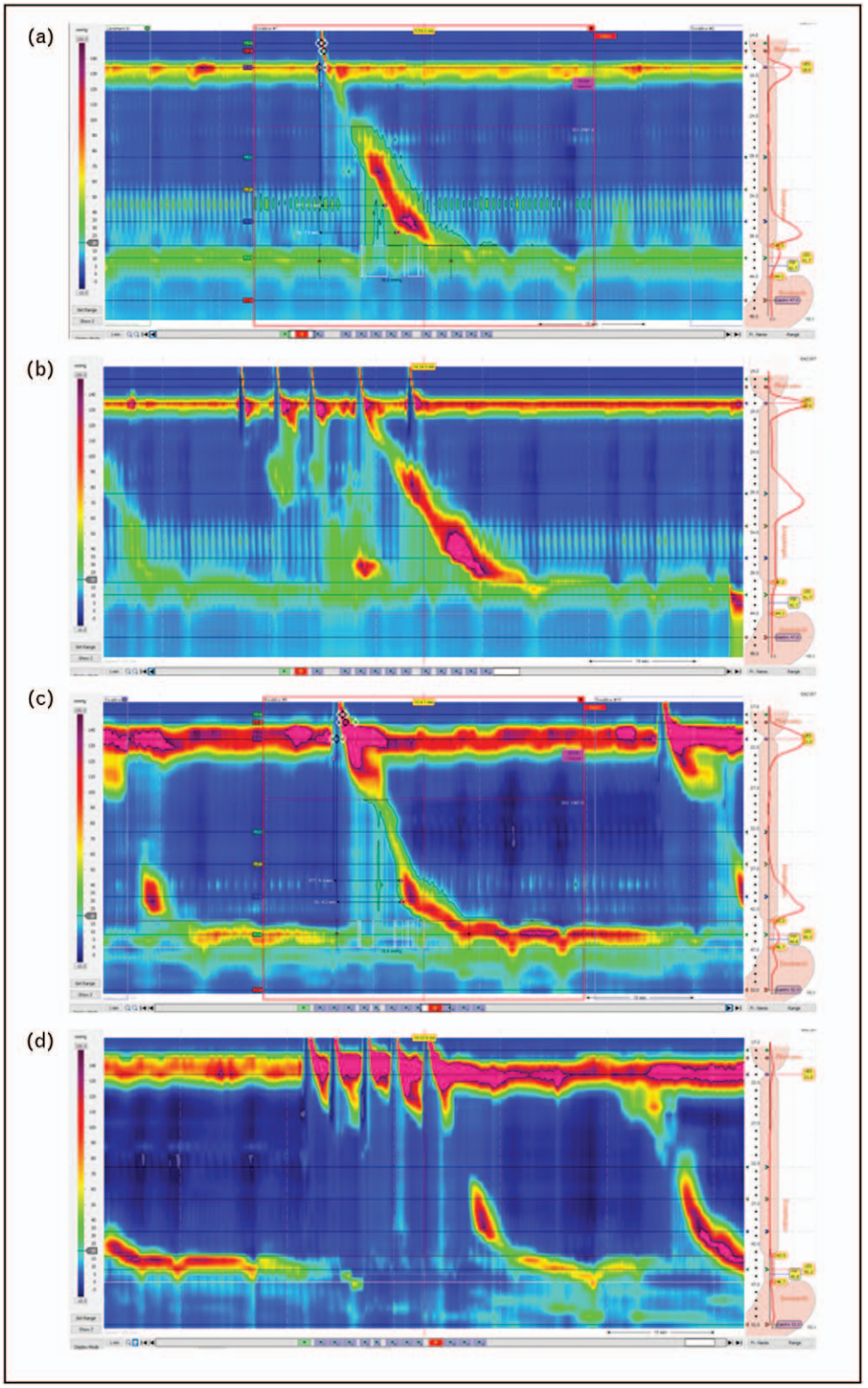

FIGURE 3. A role for MRS in detecting true EGJOO. First patient had concordant elevation of IRP with single swallows (a) and during MRS (b), whereas in the second patient (c), IRP normalized during MRS (d).

evidence of EGJOO had an EGJ-distensibility index less than 2 mm^2/mm Hg. A total of 9 of the 18 patients with radiographic evidence of EGJOO and EGJ-distensibility index less than 2 mm^2/mm Hg underwent achalasia-type treatment, and 78% of these (seven of nine) had symptomatic improvement. Of the six patients with a normal EGJ-distensibility index (>3 mm^2/mm Hg) who were treated

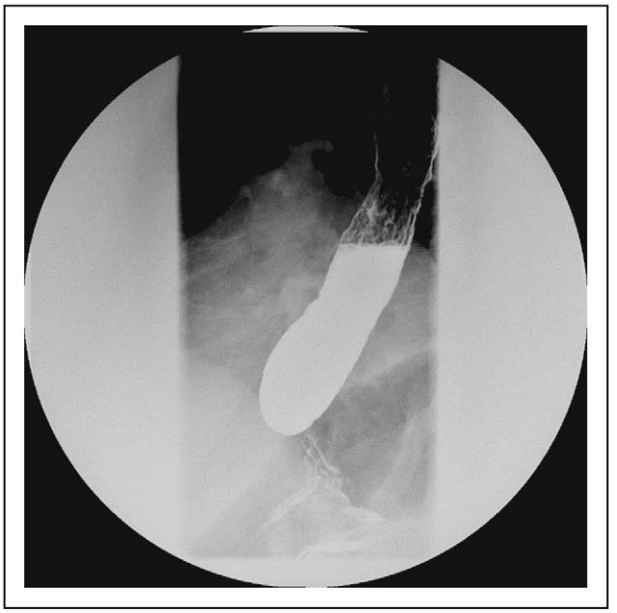

FIGURE 4. Barium esophagram image of EGJOO. There is barium retention above GEJ providing radiologic evidence for EGJOO. GEJ, gastroesophageal junction.

conservatively, all had subsequent symptomatic improvement. This study suggests that FLIP is useful in identifying patients with EGJOO who are most likely to benefit from achalasia-type therapy.

After the diagnosis of EGJOO is established, secondary causes need to be ruled out. Upper gastrointestinal endoscopy (EGD) should be performed with esophageal biopsies [1▪▪]. Also, medications should be reviewed to identify those that can cause EGJOO, particularly opiate narcotic analgesic medications.

Chicago classification version 3.0 recommended that EGJOO finding on HRM should prompt cross-sectional imaging such as computed tomography (CT) or endoscopic ultrasound (EUS) because some cases of EGJOO had been associated with submucosal EGJ tumors [2]. However, subsequent studies have shown minimal benefit from EUS studies in patients with EGJOO. In a study of 1044 patients who had HRM, 124 EGJOO patients were identified who underwent EGD and barium esophagram [19]. These procedures identified secondary causes of EGJOO including malignancy, infiltrative, and structural problems in 25% of patients, but cross-sectional imaging (CT and EUS) provided no additional diagnostic yield. In another study of 107 EGJOO patients who were followed for a period of 463 days, CT and EUS (performed in 48% of the patients) provided no useful clinical information [20].

MANAGEMENT OF ESOPHAGOGASTRIC JUNCTION OUTFLOW OBSTRUCTION

A summary of a recommended treatment approach is depicted in Fig. 6. Management of the secondary EGJOO should be focused on addressing the

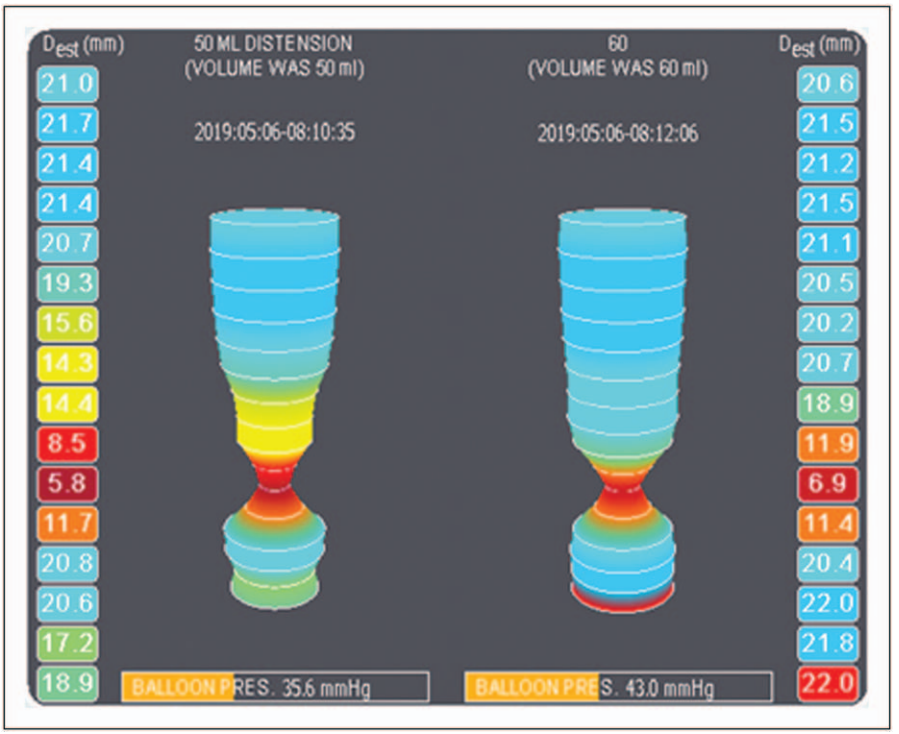

FIGURE 5. FLIP findings of EGJOO. Balloon distention to 50 ml (a) and 60 ml (b). Notice the peristaltic wave approaching LES (a) and narrow diameter at the LES (a and b). LES, lower esophageal sphincter.

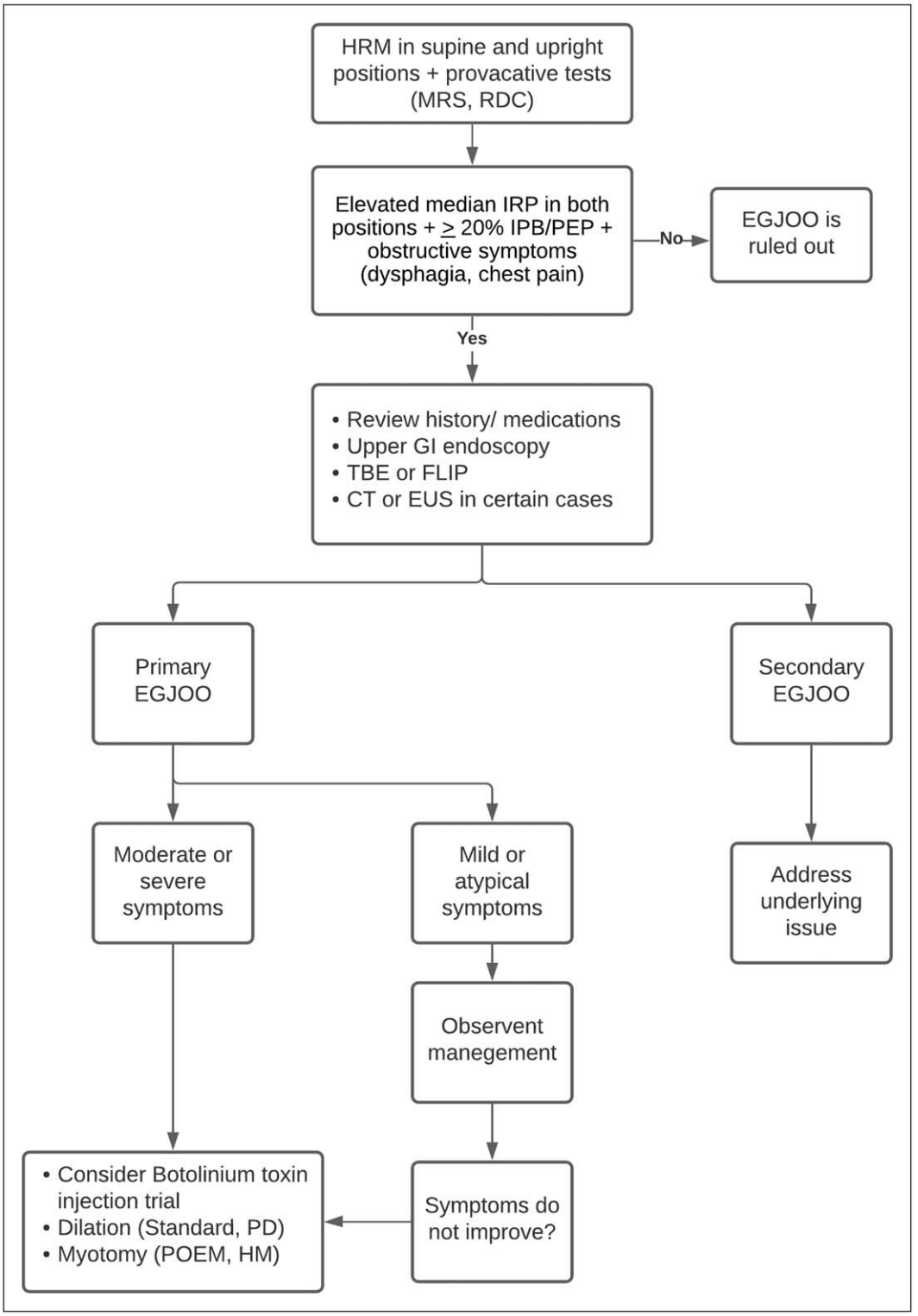

FIGURE 6. Approach to patients with EGJOO finding on HRM. CT, computed tomography; EUS, endoscopic ultrasound; FLIP, functional lumen imaging probe; HRM, high-resolution esophageal manometry; HM, Heller myotomy; IRP, integrated residual pressure; IPB, intrabolus pressure; MRS, multiple rapid swallow; PD, pneumatic dilation; PEP, panesophageal pressurization; POEM, peroral endoscopic myotomy; RDC, rapid drinking challenge; TBE: timed barium esophagram.

underlying cause. Reviewing patient's medication list and screening for illicit drug use including opioids is recommended. Cessation of opiates or other causative medications should be performed, if possible, before resorting to more aggressive measures for EGJOO [1▪▪,6].

Spontaneous resolution of EGJOO has been observed frequently (overall aggregate rate of 43%) and a conservative watchful waiting approach is reasonable for patients with mild or atypical symptoms [3▪▪].

The EGJOO patient response rate to medications has varied widely (from 0% to 75%) and medications generally are not considered first line therapy for EGJOO [1▪▪,5,15,21]. Medications that have been used for treatment of EGJOO include calcium channel blockers, nitrates, TCA, and muscle relaxants [3▪▪]. Lynch *et al.* followed 83 patients with EGJOO (11 with secondary form); 3 who received medications (amitriptyline for chest pain, hyoscyamine for dysphagia, and proton pump inhibitor (PPI) for reflux) showed improvement in symptoms after 4 months [21]. Two small studies showed improvement of symptoms after adding or increasing the dose of PPIs [5,15]. An open label study evaluated the effect of peppermint oil for 36 patients who presented who had HRM for symptoms of dysphagia or chest pain (eight patients had EGJOO) [22]. The patients with EGJOO and DES had the highest response rate. Acotiamide, an acetylcholinesterase inhibitor approved in Japan for functional dyspepsia, has shown efficacy in improving symptom scores and reducing IRP and distal contractile integral in patients with EGJOO [23].

Treatment options for primary EGJOO are similar to those for achalasia and are aimed at lowering the LES pressure. These include medications (smooth muscle relaxants), botulinum toxin (Botox) injection of the LES, esophageal dilation (standard or pneumatic dilation), and myotomy (peroral endoscopic myotomy (POEM) or Heller myotomy) [24].

Treatment response to Botox injection in patients with EGJOO is variable and studies typically have had small patient sample sizes and were not placebo controlled [25]. In one study of eight EGJOO patients, five received Botox injection with immediate improvement in all, and symptoms did not recur in three patients for 6–10 months. Pneumatic dilation was performed in the other three patients with a 33% response rate [26]. In a study of 16 patients with primary EGJOO treated with pneumatic dilation, Heller myotomy, or Botox injection, only those treated with Heller myotomy responded well [27]. In a systematic review of 8 studies, 82% of patients with primary EGJOO were given botulinum toxin injection or received no intervention (expectant management), with success rates of 58% and 54% respectively, and symptom resolution was similar for all treatment strategies [28▪▪]. The duration of Botox injection efficacy in patients with EGJOO is not clear, but it has not demonstrated long-lasting effects in patients with achalasia. In a systematic review of seven studies comparing Botox with pneumatic dilation in patients with achalasia, there was no difference in remission within four weeks, but at six months 46 of 57 in the pneumatic dilation group versus 29 of 56 in the Botox group remained in remission, and after one year, 55 of 75 in the pneumatic dilation group versus 27 of 72 in the Botox group were in remission [29]. In an older study of 36 patients with elevated IRP (>13 mmHg on HRM), all patients responded to Botox with an average of 12.8 months of symptomatic relief [30]. Botox can also be used as a therapeutic trial to identify patients who might be good candidates for more aggressive interventions like pneumatic dilation, Heller myotomy, and POEM [28▪▪].

Standard through the scope dilation and pneumatic dilation of the EGJ may both be effective treatment options for patients with symptomatic EGJOO. In four small studies, standard dilation (balloon size < 30 mm) was performed and yielded a response rate of 55–100%, although balloon sizes were not clearly defined [5,15,21,31]. Pneumatic dilation is generally the dilation technique used to treat patients with symptomatic EGJOO. A total of 33 patients with primary EGJOO and delayed esophageal emptying on TBE underwent pneumatic dilation (balloon size ≥ 30 mm) and on the post-treatment office visit in 4–6 weeks, 67% reported symptom relief, of whom 18% eventually had symptom recurrence, 6% were lost to follow up, and 9% reported no change [32]. A systematic review of eight studies reported a success rate of 58% for pneumatic dilation in EGJOO [28▪▪].

The Esophageal Functional Luminal Imaging Probe (EsoFLIP) balloon is a 30 mm hydrostatic balloon dilator that uses impedance planimetry technology for the measurement of the diameter and cross-sectional area during the dilation to help determine effective dilation [33]. This 30 mm EsoFLIP balloon was reported to achieve clinical success in two-thirds of patients with achalasia and one-third of patients with EGJOO.

Heller myotomy has shown efficacy in EGJOO in a number of small case series [3▪▪]. Scherer *et al.* identified 16 patients with primary EGJOO and 8 patients with postfundoplication dysphagia, and compared them to 68 normal controls. The EGJOO patients were treated with pneumatic dilation, Botox, and Heller myotomy, and only the three patients treated with Heller myotomy responded well [27].

There is growing interest in using POEM for EGJOO. In a prospective study of 15 EGJOO patients, treatment with POEM resulted in improvement in IRP (decrease of 17.6 mmHg) and symptoms at 6 months. Among these 15 patients, 10 had pH testing and 7 had abnormal acid reflux, with 5 having esophagitis on EGD [34]. Another study of 125 patients with a variety of motility disorders (including 8 with EGJOO) at a tertiary care center showed a clinical response in 100% of EGJOO patients post-POEM, which persisted after 12 months in 7 (88%) patients [35]. Khashab *et al.* in an international multicenter study of 50 patients with nonachalasia dysmotility (including 15 EGJOO patients) who underwent POEM showed chest pain improvement in 88.9% and overall clinical improvement in 93.3% of EGJOO patients with a median follow-up of 195 days [36].

CONCLUSIONS

As more patients undergo HRM for an increasing number of indications (e.g., perioperative evaluation for antireflux, bariatric, and lung transplant surgeries), more patients will be labeled as 'EGJOO.' Chicago classification version 4.0 has tried to address the concern of overdiagnosis of EGJOO by adding more stringent criteria including the need for obstructive symptoms and confirmation with tests other than manometry (TBE along with barium tablet or compliance measurements with FLIP) for a definitive diagnosis of EGJOO [11▪]. Once the diagnosis of EGJOO is established, secondary causes need to be evaluated, especially regarding use of opiate pain medications. There are a number of treatment options for primary EGJOO with variable response rates. Many patients improve without intervention, and an observant watchful waiting approach is recommended for patients with mild or atypical symptoms. There seems to be a limited role for medical management. Botox injection of the LES is a safe and effective (albeit temporary) treatment, and a response to Botox injection suggests that the patient might be a good candidate for more definitive treatment. pneumatic dilation and myotomy (POEM or Heller myotomy) appear to be effective modalities in treating EGJOO. Large-scaled randomized trials are now needed to determine the optimal treatment approach for patients with EGJOO.

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Conflicts of interest

There are no conflicts of interest.

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