Esophagogastric Junction Outflow Obstruction: A Diagnosis in Evolution

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Abstract: Esophagogastric junction outflow obstruction (EGJOO) is a rapidly evolving diagnosis that can represent early or variant achalasia. Since the publication of the Chicago Classification version 4.0, the criteria for this diagnosis have been more stringent. Currently, the criteria include an elevated median integrated relaxation pressure (IRP) in both the supine and upright positions, elevated intrabolus pressure in at least 20% of supine swallows, dysphagia and/or chest pain, as well as an abnormal timed barium esophagram and/or impedance planimetry testing. Additionally, other secondary causes may result in an elevated IRP and must be excluded. The management of conclusive EGJOO is targeted therapy to the lower esophageal sphincter (LES), although treatment is not straightforward. Overall, adjuvant testing and data should be scrutinized for appropriateness of LES disruption. The spectrum of treatment options includes simple monitoring as well as more invasive therapies such as endoscopic dilation and myotomy. This article explores the newest criteria and management options for clinically relevant EGJOO.

In 2021, the fourth iteration of the Chicago Classification (CCv4.0) presented a paradigm shift to esophageal motility by asserting that the manometric finding of esophagogastric junction outflow obstruction (EGJOO) requires associated testing and symptoms to be deemed clinically significant.1 Manometric EGJOO is now essentially nonactionable unless accompanied by dysphagia or chest pain, along with an abnormal timed barium esophagram (TBE) or functional lumen imaging probe (FLIP) testing. Moving beyond the silo of a manometric finding and requiring synthesis of other clinical data in EGJOO has led to increased diagnostic specificity and appropriateness of therapy. However, not all patients who meet criteria for a conclusive diagnosis of

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EGJOO require targeted therapy of the lower esophageal sphincter (LES). This article discusses the most current literature and expert opinions regarding this evolving diagnosis.

**Background**

The manometric finding of EGJOO was defined per the Chicago Classification version 3.0 (CCv3.0) as impaired deglutitive LES relaxation with some intact peristalsis, not meeting criteria for achalasia. Given the complex nature of the interaction among the LES, crural diaphragm, and phrenoesophageal ligament at the esophagogastric junction (EGJ), this manometric finding was reported in up to 24% of patients undergoing high-resolution esophageal manometry (HRM). Plentiful secondary causes ranged from structural sources, such as a hiatal hernia or catheter artifact, to medication effects (Table). Symptoms in these patients varied widely, with the most common symptoms being dysphagia, chest pain, heartburn, and regurgitation.

**Manometric Diagnosis**

The CCv4.0 focused on narrowing the criteria for EGJOO to decrease false positives and more precisely tailor therapies. A conclusive diagnosis of EGJOO now requires some intact peristalsis in the setting of an elevated median integrated relaxation pressure (IRP) in both the supine and upright positions, elevated intrabolus pressure (ie, supine distal esophageal pressurization at ≥20 mm Hg isobaric contour) in at least 20% of supine swallows, dysphagia and/or chest pain, as well as an abnormal TBE and/or FLIP testing. Secondary causes (eg, structural, infiltrative, inflammatory, medication-related) should be ruled out, typically at minimum via barium esophagram and upper endoscopy.

Several studies of varying sizes have demonstrated minimal added yield of routine cross-sectional imaging. In a study of more than 100 patients with EGJOO based on CCv3.0, all secondary causes were found on upper endoscopy and/or barium esophagogram with no additional causes revealed on computed tomography (CT) scan or endoscopic ultrasound. Furthermore, 2 patients had false-negative findings on CT scan. As such, the regular use of cross-sectional imaging in these patients may not be merited but can be considered if there is a high clinical suspicion for malignancy.

**Further Manometric Considerations**

HRM pressure topography provides much information in addition to peristaltic activity and sphincter tone. Additional parameters may help identify patients with EGJOO who could benefit from targeted LES treatment, including pattern of peristalsis, provocative esophageal testing, and pharmacologic provocation.

The CCv4.0 suggests describing EGJOO in the context of the pattern of peristalsis, including EGJOO with spastic features, with hypercontractile (HC) features, with ineffective motility, or with no evidence of disordered peristalsis, as noted in Figure 1. Clinical observation as well as case series note that EGJOO patients with spastic or HC features are more likely to progress toward clinically significant disease. These findings were substantiated in a recent investigation performed at the University of Pennsylvania, which found that EGJOO with spastic and/or HC features was associated with an increased odds of abnormal confirmatory testing (odds ratio, 8.35; 95% CI, 1.40-49.89; *P*=.02), whereas EGJOO with ineffective motility was not (odds ratio, 1.86; 95% CI, 0.29-11.76; *P*=.51). Provocative testing on esophageal manometry such as the rapid drink challenge (RDC) and solid test meals is utilized frequently in EGJ characterization. The CCv4.0 recommends that the RDC is performed during routine HRM. Patients briskly swallow 200 mL of liquid in an upright position, normally resulting in deglutitive inhibition. However, lack of LES relaxation as well as premature or HC swallows may indicate EGJ dysfunction. Additionally, panesophageal pressurization (PEP) during RDC is often seen in patients with EGJOO who evolve to achalasia. A recent study of 97 EGJOO patients based on the CCv3.0 noted that symptomatic patients with an Eckardt score greater than 3 were likely to have PEP or abnormal motility during RDC that was not elucidated.
on routine swallows. PEP has also been shown to correlate with more severe symptoms in these patients. HRM with a solid test meal may also elucidate motility disorders in patients with borderline testing, especially in patients with dysphagia.

Pharmacologic LES relaxation has been used to further assess the EGJ, particularly in patients with LES disorders. Amyl nitrate can result in an IRP reduction of 10 mm Hg in patients with LES smooth muscle inhibitory dysfunction. Additionally, cholecystokinin has resulted in a paradoxical LES contraction greater than 50 mm Hg in patients with achalasia. Although frequently described, these pharmacologic provocations are uncommonly used in clinical practice, given both safety concerns and lack of availability.

Timed Barium Esophagram

Barium esophagram is a widely employed, low-risk, and low-cost evaluation to assess esophageal clearance and the anatomy and function of the EGJ. Although protocols vary, most commonly the TBE requires patients to drink 200 to 250 mL of barium in the standing position followed by images taken at 1, 2, and 5 minutes. Then, patients are often instructed to swallow a barium tablet. Although barium esophagram has been well established to have high specificity in ruling in achalasia, the criteria for a dysfunctional EGJ vary widely across studies. Tablet impaction and a barium column greater than 5 cm tall at 5 minutes are widely accepted as abnormal, yet some studies report positive tests with any retention at 1 to 5 minutes, and other studies look specifically for a corkscrew or beaked appearance. Additionally, further studies have explored the potential for significance in the change in esophageal surface area on barium esophagram.

Given the wide range of patient presentations and outcomes in EGJOO according to the CCv3.0, numerous studies have evaluated the use of barium esophagram in these patients. In a study of 309 patients who
underwent TBE and HRM, a column height of at least 6 cm at 1 minute and at least 2 cm at 5 minutes differentiated untreated achalasia from EGJOO with noteworthy accuracy (at 1 minute, sensitivity of 91% and specificity of 56%; at 5 minutes, sensitivity and specificity of 84%). The addition of a barium tablet increased the diagnostic yield from 80% to 100% in untreated patients with achalasia and 49% to 60% in patients with EGJOO. However, this study was unable to reliably differentiate EGJOO from nonachalasia motility disorders. Additionally, several studies have confirmed that patients with CCv3.0-defined EGJOO with significant barium retention were more likely to have an elevated upright IRP. By contrast, a study by van Hoeij and colleagues evaluated 47 patients with CCv3.0-defined EGJOO, of whom 25 underwent TBE and 3 eventually developed achalasia. However, barium retention in these patients was not found to be predictive of progression or treatment response.

Overall, TBE is a safe and well-established method to evaluate LES dysfunction and rule in achalasia. This radiographic test has substantial potential in guiding treatment selection and response in manometric EGJOO. Further studies in this realm are forthcoming.

### Functional Lumen Imaging Probe

The FLIP is a catheter-based device that utilizes impedance planimetry to evaluate the pressure and cross-sectional area of hollow organs. These measurements are used to assess esophageal distensibility, compliance, and contractile response. FLIP testing has been especially useful in assessing physiology and treatment response in patients with achalasia. Given the precision with which the LES is assessed by impedance planimetry, FLIP can clarify characteristics of the EGJ in manometric EGJOO. Reduced opening of the EGJ on FLIP (defined as EGJ distensibility index [EGJ-DI] <2.0 mm²/mm Hg at the 60 cc fill volume and a maximum EGJ diameter <12 mm using the 16 cm balloon [EF-322N]) has been suggested to indicate true physiologic obstruction.

An investigation by Beveridge and colleagues evaluated 20 patients with EGJOO based on CCv3.0 who underwent FLIP. In patients with reduced EGJ-DI, botulinum toxin injection treatment was administered to the LES. The mean Eckardt score improved more in the patients who underwent botulinum toxin injection than in patients who did not. Similarly, a larger retrospective study of 139 patients with inconclusive EGJOO based on CCv4.0 also evaluated FLIP findings and response to therapy. Patients with reduced EGJ-DI on FLIP had more improvement in Eckardt score with achalasia-type therapies (77%), including Heller myotomy, peroral endoscopic myotomy (POEM), pneumatic dilation (PD), and botulinum toxin injection, than with nonachalasia-type therapies (0%). Furthermore, a retrospective study of 722 patients who underwent both HRM and FLIP revealed that 90% of patients with reduced EGJ opening on FLIP had achalasia or significant EGJOO (elevated IRP in multiple positions and an abnormal TBE). Additionally, of the 187 patients with normal EGJ opening, only 1 patient had achalasia or significant EGJOO, further supporting the utility of EGJ-DI evaluation in patients with possible EGJOO. Overall, FLIP is a useful complementary tool in evaluating EGJ opening dynamics via the EGJ-DI and has potential in guiding treatment selection and response in patients with EGJOO.

### Management

It is critical to note that invasive treatment for this manometric finding should not be considered if conclusive EGJOO is not established. Additionally, even in patients with conclusive EGJOO, early or variant achalasia is not assured. Given the heterogeneity of the clinical course of EGJOO, continued monitoring and repeat testing may be required to clarify the diagnosis. Overall, adjuvant testing and data should be scrutinized for appropriateness of LES disruption before proceeding, as no therapy is without risk and some therapies are irreversible.

Pharmacologic therapy such as smooth muscle relaxants, proton pump inhibitors (PPIs), tricyclic antidepressants, and antispasmodics has been employed for the manometric finding of EGJOO based on CCv3.0 with varied results. One small study reported 3 of 4 patients with symptomatic improvement at a median of 4 months (tricyclic antidepressants for chest pain, hyoscyamine for dysphagia, PPIs for reflux). However, outcomes across studies range, with patients noting lasting symptom relief at 3 to 6 months in 0% to 75% of patients. Placebo-controlled studies with large sample sizes of patients who meet the most updated criteria for EGJOO are lacking. Thus, it is reasonable to consider pharmacotherapy in borderline cases if side effect profiles are favorable, while acknowledging the paucity of controlled data.

Botulinum toxin injection of the LES is a low-risk intervention that is widely utilized given its simplicity of administration. Several case series of patients with EGJOO have noted positive responses to botulinum toxin injection to date. In patients with CCv3.0-defined EGJOO with dysphagia or chest pain, short-term relief (<6 months) was reported in up to 100% of patients and sustained symptomatic relief of at least 6 months in up to 67% of patients. A case series of 11 patients...
noted that 64% of patients with dysphagia and evidence of LES dysfunction on barium esophagram had sustained symptomatic relief at 2 years. However, there are no controlled trials comparing botulinum toxin injection with sham procedures. Thus, it is difficult to conclude the exact therapeutic effects of botulinum toxin injection. However, this therapy may be considered in patients with EGJOO, with the understanding that response durability may be limited.

Standard through-the-scope and bougie-type esophageal dilations have not resulted in notable symptomatic relief for the majority of patients with CCv3.0-defined EGJOO. Case series have revealed symptomatic relief in a limited number of patients, reported in up to 35% of treated patients. Meanwhile, PD has demonstrated slightly more success as targeted LES therapy in EGJOO. POEM has similarly been successful in small and uncontrolled studies. Symptomatic relief in patients with EGJOO after POEM ranges from 71% to 100% of patients reporting symptomatic improvement via the Eckardt score. Filicori and colleagues noted that 100% of the 14 patients with EGJOO with chest pain by Clayton and colleagues observed 33 patients with CCv3.0-defined EGJOO with dysphagia and abnormal TBE. Almost 80% of patients who underwent PD experienced sustained symptom improvement for up to 5 years.

Limited uncontrolled data on surgical myotomies, including laparoscopic and robotic-assisted ones, have revealed noteworthy symptomatic relief in patients with EGJOO based on CCv3.0. Although sample sizes were quite small, all studies noted 100% of patients with symptomatic relief of dysphagia and/or chest pain at 12 months or longer.

Figure 2. Flowchart of suggested management of esophagogastric junction outflow obstruction.

EGJ, esophagogastric junction; FLIP, functional lumen imaging probe; IBP, intrabolus pressure; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; PD, pneumatic dilation; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor; SM, smooth muscle; TBE, timed barium esophagram; TCA, tricyclic antidepressant.

*Personalized approach based on level of suspicion for a primary motility disorder.
or dysphagia who underwent POEM had an improvement in esophageal emptying on barium esophagram and symptoms via the Eckardt score at 6 months. The majority (80%) of patients had sustained improvement in symptoms at a median of 48 months. However, postprocedure gastroesophageal reflux symptoms are commonly reported. Post-POEM gastroesophageal reflux disease has been demonstrated in up to 40% of patients, but can be reduced to 0% to 13% with PPI therapy. Overall, expert opinion has noted that esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0. Neurogastroenterol Motil. 2021;33(1):e14058.

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References


Conclusion and Future Directions

Initially a manometric finding, EGJOO has evolved into a diagnosis made only after thorough clinical assessment, exclusion of secondary causes, esophageal manometry, and TBE or FLIP testing. However, this is not a straightforward finding, and adjuvant testing should be scrutinized for appropriateness of LES disruption. The spectrum of treatment options includes monitoring as well as more invasive therapies such as endoscopic dilation and myotomy. Studies investigating characteristics of patients with treatment-responsive EGJOO are critical in guiding future management.

Disclosures

Dr Lynch has served as a consultant for Medtronic and on advisory boards for Regeneron, Phathom Pharmaceuticals, and Sanofi. Dr Chen has served as a consultant for Phathom Pharmaceuticals. Dr Jain has an institutional consulting agreement with Medtronic and has served on advisory boards for AstraZeneca and Sanofi. Dr Yadlapati has served as a consultant for Medtronic, Phathom Pharmaceuticals, Braintree Pharmaceuticals, Reckitt Benckiser Healthcare Ltd, and StatLinkMD; has received research support from Ironwood Pharmaceuticals; and has served on an advisory board for RJS Mediagnostix with stock options.

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