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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Clinical Practice Update: The Use of Per-Oral Endoscopic Myotomy in Achalasia: Expert Review and Best Practice Advice From the AGA Institute

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The purpose of this review is to describe a place for per-oral endoscopic myotomy (POEM) among the currently available robust treatments for achalasia. The recommendations outlined in this review are based on expert opinion and on relevant publications from PubMed and EMbase. The Clinical Practice Updates Committee of the American Gastroenterological Association proposes the following recommendations: 1) in determining the need for achalasia therapy, patient-specific parameters (Chicago Classification subtype, comorbidities, early vs late disease, primary or secondary causes) should be considered along with published efficacy data; 2) given the complexity of this procedure, POEM should be performed by experienced physicians in high-volume centers because an estimated 20−40 procedures are needed to achieve competence; 3) if the expertise is available, POEM should be considered as primary therapy for type III achalasia; 4) if the expertise is available, POEM should be considered as treatment option comparable with laparoscopic Heller myotomy for any of the achalasia syndromes; and 5) post-POEM patients should be considered high risk to develop reflux esophagitis and advised of the management considerations (potential indefinite proton pump inhibitor therapy and/or surveillance endoscopy) of this before undergoing the procedure.

Keywords: Achalasia; Esophageal Motility Disorders; High-Resolution Manometry; Per-Oral Endoscopic Myotomy.

Within the past decade, per-oral endoscopic myotomy (POEM) has evolved from an exciting concept[1] to a mainstream treatment option for achalasia. Indeed, the pioneering Japanese center for refining the technique recently summarized technical pearls and pitfalls on performing POEM gleaned from their first 1000 procedures.[2] Uncontrolled outcomes data have been very promising comparing POEM with the standard surgical treatment for achalasia, laparoscopic Heller myotomy (LHM).[3] However, concerns remain regarding post-POEM reflux, the durability of the procedure, and the learning curve for endoscopists adopting the technique. Coupled with a recent randomized controlled study comparing pneumatic dilation (PD) and LHM reporting equivalent (excellent) 5-year outcomes,[4,5] the role of POEM in achalasia treatment remains controversial. The purpose of this commentary is to describe when clinicians should consider POEM among the robust therapies currently available for achalasia.

Expansion of the Indications for Lower Esophageal Sphincter Myotomy

High-resolution manometry (HRM)[6,7] and the development of the Chicago Classification, now in its third iteration,[8] have substantially revised the classification of esophageal motility disorders. Nowhere is this more evident than in our concept of achalasia, now differentiated into 3 subtypes and a fourth entity, esophagogastric junction (EGJ) outflow obstruction, which can mimic achalasia in terms of clinical presentation and management.[9–12] A Chicago Classification diagnosis of achalasia stipulates both impaired deglutitive EGJ relaxation and absent peristalsis. However, absent peristalsis does not preclude esophageal pressurization or non-peristaltic contractility and these are quite common in achalasia. In fact, the achalasia subtypes are defined by different patterns of esophageal contractility that accompany impaired EGJ relaxation: type I, with negligible pressurization within the esophagus, often referred to as classic achalasia; type II, with panesophageal pressurization, wherein uniform simultaneous pressurization bands span from the upper sphincter to the lower sphincter; or type III, with premature (spastic) contractions, wherein the latency between upper sphincter relaxation and arrival of a rapidly propagated contraction at the distal esophagus is $<$4.5 seconds.[13] In multiple reported series, type II achalasia is the most common presenting subtype.

A fundamental difficulty in diagnosing achalasia is that there is no biomarker for the disease. Although the classical pathology is inflammation of the myenteric plexus leading to aganglionosis,[13,14] the diagnosis is not established by biopsy and atypical cases clearly exist.[15] The diagnosis is usually established using HRM to demonstrate that some combination of dysphagia, regurgitation, and chest pain is occurring as a result of absent peristalsis and nonmechanical

Abbreviations used in this paper: EGJ, esophagogastric junction; HRM, high-resolution manometry; IRP, integrated relaxation pressure; LHM, laparoscopic Heller myotomy; LES, lower esophageal sphincter; POEM, per-oral endoscopic myotomy; PD, pneumatic dilation.

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esophageal outflow obstruction.[16] Consequently, there are 2 fundamental limitations of the Chicago Classification criteria for achalasia: 1) the integrated relaxation pressure (IRP), used to define the adequacy of deglutitive lower esophageal sphincter (LES) relaxation,[17,18] can be less than the upper limit of normal in achalasia (eg, the IRP is <100% sensitive), particularly in type I disease[19,20]; and 2) there can be instances with preserved peristalsis (eg, Chicago Classification criteria are <100% specific). Furthermore, the disease evolves over a variable timespan leaving open the possibility that testing is done somewhere along the continuum from normal function to unequivocal achalasia when the requisite diagnostic thresholds are not met, for example, early or incompletely evolved disease. Early in the disease, maneuvers that unmask impaired inhibitory innervation, such as multiple rapid swallows or a rapid drink challenge, may be useful in supporting a diagnosis of achalasia.[21–23] Conversely, late in the disease, both the LES pressure and IRP might be very low, thereby suggesting a diagnosis of absent contractility, with an achalasia diagnosis established by using functional luminal imaging probe technology and presence of stasis on the barium esophagram.[20]

In addition to the 3 achalasia subtypes, the Chicago Classification recognizes EGJ outflow obstruction as another syndrome in which sphincter dysfunction can cause dysphagia. With EGJ outflow obstruction, the IRP is greater than the ULN, but the "absent peristalsis" criterion for achalasia is not met. Peristalsis may be fragmented or even normal. EGJ outflow obstruction is a heterogeneous group with a spectrum of potential etiologies, including incompletely expressed or early achalasia or an isolated disorder of impaired LES relaxation. Alternatively, EGJ outflow obstruction may also be secondary to esophageal wall stiffness from an infiltrative disease or cancer, eosinophilic esophagitis, vascular obstruction, sliding or paraesophageal hiatal hernia, abdominal obesity, or the effects of opiates.[9,24] Consequently, EGJ outflow obstruction always requires more intense clinical evaluation to clarify its etiology (eg, endoscopic ultrasound, computed tomography, timed barium esophagram). Prior surgery should also be considered as similar manometric findings can be found after anti-reflux or bariatric surgery, sometimes making it very difficult to establish cause and effect.[25,26] The natural history and heterogeneity of EGJ outflow obstruction was studied in 4 recent series reporting that many of these patients were minimally symptomatic or asymptomatic, that in 20%–40% of cases the "disorder" resolved spontaneously, but that 12%–40% of them end up being treated as achalasia.[10–12,27] Finally, another disorder often associated with EGJ outflow obstruction is hypercontractile (jackhammer) esophagus. A recent meta-analysis cited a 72% success rate of POEM for this disorder.[28] Although seemingly a disorder of the esophagus proximal to the LES, our opinion is that LES myotomy should be done concomitantly if POEM is applied in these patients.

Evident from the preceding discussion, treating "achalasia" is not limited to treating achalasia, as it would be defined by histopathology. Rather, the clinical evaluation concludes that clinically relevant EGJ outflow obstruction exists as a cause of dysphagia and that the patient is likely to benefit from a therapy targeting that outflow obstruction (eg, an achalasia treatment). This emphasizes a very important limitation of existing data regarding achalasia treatments. Historically, there has been minimal consistency in characterizing the treatment populations and existing treatment data lag substantially behind the current diagnostic considerations detailed here. Consequently, there are several instances in which the published data on treating achalasia need to be interpreted in the context of patient-specific variables.[29] Table 1 summarizes the spectrum and characteristics of achalasia syndromes potentially amenable to achalasia treatments.

Per-Oral Endoscopic Myotomy vs Laparoscopic Heller Myotomy: Strengths and Weaknesses

Coincident with the widespread adoption of the Chicago Classification came the development of POEM,[30] posing the question of why POEM might be considered an advancement over LHM. The POEM procedure allows for performing a myotomy of the LES using endoscopy rather than laparoscopy (as with LHM). The procedure involves making a mucosal incision 10–15 cm proximal to the LES and creating a submucosal tunnel from there, extending distally 2–4 cm onto the gastric cardia using a standard endoscope and electrocautery. A circular muscle myotomy is then achieved from within the submucosal tunnel, beginning at least 2–3 cm distal to the mucosotomy and progressing to the distal point of cardia dissection.[31] Obvious technical advantages of POEM over LHM include lack of abdominal incisions, more rapid recovery, and the option of avoiding general anesthesia with airway intubation. Other, more subtle, advantages include the ease of performing a longer myotomy if desired (because mediastinal dissection is unnecessary), avoidance of vagal nerve injury, and lack of intra-abdominal adhesions that might hinder future surgery. Another ostensible advantage of POEM over LHM is that it is done without gastroesophageal junction dissection. To accurately perform LHM, the EGJ must first be surgically isolated, which entails division of the phrenoesophageal ligament and short gastric vessels, both important anti-reflux mechanisms maintaining the angle of His. Consequently, a posterior (Toupet) or anterior (Dor) fundoplication is typically performed in conjunction with LHM,[32] leaving open the potential for post-LHM fundoplication-related complications, especially obstructive dysphagia, given the aperistaltic esophagus of achalasia.

The widespread adoption of the POEM procedure has been a major shift in achalasia therapeutics. The reported success rate of POEM in multiple uncontrolled studies has been >90% (Table 2).[30,33–44] Inoue et al[30] reported the largest series, a cohort of 500 POEM patients, and found a significant reduction in Eckardt scores and LES pressures at 2 months, 1 year, and 3 years post-procedure. Similar patient outcomes have been reported for POEM in patients with prior PD or LHM.[45–46] Serious adverse events with POEM include

Table 1. Clinical Achalasia Syndromes Within and Beyond Chicago Classification, Version 3.0[a]

Syndrome	Median IRP	Esophageal contractility	Qualifications/notes
CC: type I achalasia	Greater than ULN	Absent contractility	Most published treatment trials excluded end-stage cases
CC: type II achalasia	Greater than ULN	Absent peristalsis Panesophageal pressurization with ≥20% of swallows	Most common presenting achalasia subtype Often misdiagnosed before HRM because of esophageal shortening and pseudorelaxation
CC: type III achalasia	Greater than ULN	Absent peristalsis Premature contractions with ≥20% of swallows	Often mistaken for spasm before HRM Obstructive physiology includes the distal esophagus
CC: EGJ outflow obstruction	Greater than ULN	Sufficient peristalsis to exclude types I, II or III achalasia	Can be early or incomplete achalasia (12%−40%) Can resolve spontaneously Can be artifact; further imaging of EGJ may clarify diagnosis
CC: absent contractility	Less than ULN	Absent contractility	Abnormal FLIP distensibility index or esophageal pressurization with swallows or MRS supports an achalasia diagnosis
CC: distal esophageal spasm	Normal or increased	≥20% premature contractions (DL <4.5 s)	May be evolving type III achalasia
CC: jackhammer	Normal or increased	≥20% of swallows with DCI >8000 mm Hg/s/cm	May be evolving type III achalasia if DL <4.5 s with ≥20% swallows
Opioid effect:	Greater than ULN	Normal, hypercontractile, or premature	Can mimic EGJ outflow obstruction, type III achalasia, DES, or jackhammer
mechanical obstruction:	Normal or increased	Absent, normal, or hypercontractile	EUS or CT imaging of the EGJ may clarify the etiology

CC, Chicago Classification; CT, computed tomography; DCI, distal contractile integral; DES, distal esophageal spasm; DL, distal latency; EUS, endoscopic ultrasound; FLIP, functional luminal imaging probe; MRS, multiple repetitive swallows; ULN, upper limit of normal.
[a]Apart from the achalasia subtypes, these syndromes are not specific for achalasia and may have distinct pathophysiology, but instances occur in which they are optimally managed as if they were achalasia.

perforation, pneumothorax, and bleeding. A multicenter comprehensive analysis of 1826 patients reported mild, moderate, and severe adverse events occurring with frequencies of 6.4%, 1.7%, and 0.5%, respectively.[47] One of the greatest concerns after POEM is reflux, evidence of which is observed in up to 58% of patients (Table 2).[42]

Data comparing POEM to either LHM or PD are still very limited. To date, there have been no randomized studies comparing POEM to LHM and only 1 study, reported as an abstract, comparing POEM to PD[33] (Table 2). These data suggest the efficacy of POEM to be similar to that of LHM, but with less post-procedure pain and a faster return to daily living with POEM. A recent systematic review and meta-analysis comparing outcomes of POEM (1958 patients) and LHM (5834 patients) found POEM to be more effective than LHM in relieving dysphagia in the short term (mean follow-up 16 months), but associated with a very high incidence of pathologic reflux (odds ratio of 9.31 for erosive esophagitis).[48] One recent multicenter randomized controlled trial compared POEM to PD in patients with treatment-naïve achalasia.[33] After 1 year, 92% of the POEM patients (n = 67) were in clinical remission vs 70% after pneumatic dilation (n = 66) ($P < .01$). One perforation occurred after pneumatic dilation and no severe adverse events occurred related to POEM.

A major concern with POEM has been the high rate of gastroesophageal reflux, despite the theoretical advantages of avoiding the EGJ dissection required for LHM. In the randomized controlled trial comparing POEM to PD, endoscopy 1 year after treatment found reflux esophagitis in 48% of the POEM patients (40.0% grade Los Angeles A or B, 8.3% grade C or D) compared to 13% of those treated with pneumatic dilation (all grade A or B) ($P = .02$). Similarly, a multicenter case-control series studying 282 patients found endoscopic or pH-metry evidence of post-POEM gastroesophageal reflux disease in 58% of the patients, including endoscopic esophagitis in 23% (proton pump inhibitor use was uncontrolled).[42] Furthermore, a substantial percentage of these patients are asymptomatic, despite the presence of erosive esophagitis. Illustrative of that, Werner et al[49] reported that 31% of patients with a good clinical outcome and no reflux esophagitis on their first post-POEM endoscopy developed esophagitis at a subsequent surveillance endoscopy done at a mean follow-up of 29 months, with 2 having new histologically confirmed short-segment Barrett's esophagus. As a result, routine endoscopy to screen for erosive disease or Barrett's esophagus at some point post-POEM is advocated by several leading experts.[42,49,50] Consistent with this, patients considering POEM should be advised beforehand that they might require lifelong proton pump inhibitor therapy for symptomatic reflux or erosive esophagitis. Clearly, more treatment data are needed to determine the long-term efficacy and complications of POEM. However, clinical interest is high, and a

Table 2. Reported Per-Oral Endoscopic Myotomy Treatment Data, Stratified By Quality of Evidence

First author, year	Comparison, n	Follow-up, *mo*	Post-treatment reflux, %	Efficacy, %
Randomized controlled trials				
Ponds,[33] 2017	POEM 67 PD 66	12	POEM esophagitis, 40 PD esophagitis, 13.1	POEM 92 PD 70
Nonrandomized comparisons, LHM vs POEM				
Bhayani,[34] 2014	POEM 37 LHM 64	6	POEM 39 LHM 32	POEM 100 LHM 92
Chan,[35] 2016	POEM 33 LHM 23	>6	POEM 15 LHM 26	POEM 100 LHM 87
Kumbhari,[36] 2015	POEM 49 LHM 26	9	POEM 39 LHM 46	POEM 98 LHM 81
Schneider,[37] 2016	POEM 42 LHM 84	12	Not reported	POEM 91 LHM 84
Teitelbaum,[38] 2013	POEM 17 LHM 12	Not reported	POEM 17 LHM 31	POEM 100 LHM 87
Author	Series, n	Mean follow-up, mo	Adverse events, %	Symptom improvement, %
Uncontrolled trials (>100 patients, ≥12 month follow-up)				
Cai,[39] 2014	100	11.5	0	97
Familiari,[40] 2016	100	11	0	95
Hungness,[41] 2016	115	19	3	92
Inoue,[30] 2015	500	>36	3	89
Kumbhari,[42] 2017	282	12	58 GER[a]	94
Ngamruengphong,[43] 2017	205	31	8	91
Ramchandani,[44] 2016	200	12	0	92

GER, gastroesophageal reflux.
[a]All patients were studied with pH-metry after POEM.

search of ClinicalTrials.gov on June 15, 2017 found 6 ongoing randomized controlled trials: 3 comparing POEM to PD, 2 comparing POEM to LHM, and 1 comparing POEM to botox. Hopefully, more data will be forthcoming.

In summary, POEM appears to be a safe, effective, and minimally invasive management option in achalasia in the short term; data on the long-term durability of POEM are not yet available. Given the complexity of this procedure, it should be performed by experienced physicians in high-volume centers because an estimated 20−40 procedures are needed to achieve competence and 60 to achieve mastery.[51,52] Existing uncontrolled reports suggest efficacy equal to or superior to LHM and emerging RCT data suggest POEM to be more effective than PD, but more likely to result in post-treatment reflux.

Phenotype-Directed Treatment: Where Does Per-Oral Endoscopic Myotomy Stand?

While all of the achalasia syndromes share the common element of clinically relevant EGJ outflow obstruction (Table 1), the associated pattern of esophageal contractility varies from absent contractility at one extreme to spastic contractions or normal peristalsis at the other. Indeed, in the original description of achalasia phenotypes, it was noted that an important distinction among phenotypes was in the likelihood that they would respond to achalasia treatments.[53] Treatment outcomes were best in type II achalasia and worst in type III achalasia. Subsequent reports of patients treated by LHM, pneumatic dilation, or in a randomized controlled trial comparing pneumatic dilation to LHM have confirmed these observations.[54–56] This is especially true with type III achalasia, characterized by obstructive contractility of the distal esophagus, and noted to have less-robust outcomes with therapies limited to the LES. Therein lies a unique attribute of POEM; the myotomy can be made longer if desired, potentially involving the entire smooth muscle esophagus. The length of myotomy can be gauged by HRM, esophageal wall thickening on endoscopic ultrasound, or intraoperative functional luminal imaging probe. Supportive of this, a recent meta-analysis of uncontrolled POEM series reported a weighted pooled response rate of 92% (95% confidence interval, 84%−96%) in type III achalasia with the length of myotomy averaging 17.2 cm.[57]

In addition to achalasia subtype, there are other clinical factors to consider in devising the optimal management strategy. Relevant features to consider are the severity of esophageal dilation and sigmoid deformation, the presence of hiatus hernia, presence of a significant epiphrenic diverticulum, and, for some of the achalasia syndromes, mechanical esophageal outflow obstruction. Patients with

Table 3. Treatment Considerations for Achalasia and Achalasia Syndromes

Syndrome	Preferred treatment, comments, and rationale
Type I and II achalasia	PD and LHM are both highly efficacious in RCT; PD has less morbidity and cost With PD, anticipate repeat dilations over the years Insufficient data on efficacy of POEM for advanced esophageal dilation, sigmoidization, epiphrenic diverticulum, and hiatal hernia POEM highly efficacious in RCT vs PD; only short-term data available Expect more reflux after POEM, especially with hiatal hernia
Type III achalasia	POEM, calibrate the myotomy length to the spastic segment imaged on HRM or thickened segment on EUS
EGJ outflow obstruction	Many cases resolve spontaneously Image the EGJ (EUS, CT) to rule out obstruction If achalasia therapies are applied, consider it type II achalasia
Absent contractility deemed to be achalasia	Use FLIP, timed barium esophagram, or multiple repetitive swallows on HRM to establish need for treatment If achalasia therapies are applied, consider it type I achalasia
DES deemed to be achalasia	If achalasia therapies are applied, consider it type III achalasia POEM, calibrate the length of myotomy to the spastic segment as imaged on HRM or thickened segment on EUS
Opioid effect	First choice, discontinue opioid; second choice: botox; third choice: POEM Time course of reversal with opioid cessation is not known
Obstruction	Many entities mimic achalasia, sometimes termed *pseudoachalasia*: eosinophilic esophagitis, cancer, reflux stricture, post-myotomy stricture Conventional dilation Operative reversal if relevant; directed medical therapy if relevant

NOTE. See Table 1 for defining criteria.
DES, distal esophageal spasm; EUS, endoscopic ultrasound; FLIP, functional luminal imaging probe; RCT, randomized controlled trial.

end-stage achalasia have been treated successfully with POEM,[58] but there are minimal data comparing it to LHM as initial sphincter-directed therapy in that scenario. One report suggests a doubling of adverse events with POEM in patients with sigmoid esophagus.[59] Table 3 outlines distinguishing treatment considerations among the achalasia syndromes, along with preferred treatment options and rationale for each. Note that the suggestions made are based on expert opinion, given that no existing treatment trial has ever stratified patients to this degree.

Conclusions

It is now recognized that the cardinal feature of achalasia, impaired LES relaxation, can occur in several disease phenotypes: without peristalsis, with premature (spastic) distal esophageal contractions, with panesophageal pressurization, or with peristalsis. Furthermore, physiologic testing with HRM, and sometimes functional luminal imaging probe, reveals a number of syndromes not meeting Chicago Classification criteria for achalasia that may also benefit from therapies formerly reserved for achalasia. We now conceptualize achalasia syndromes as involving the LES with or without obstructive physiology of the distal smooth muscle esophagus. A major implication of this shift is an expansion of the role of achalasia therapies toward rendering treatment in a phenotype-specific manner. This is now particularly relevant with the development of POEM, a minimally invasive technique for performing a calibrated myotomy of the esophageal circular muscle and available data do suggest POEM to be the preferred treatment option in type III achalasia when a longer myotomy is indicated. For other achalasia syndromes, POEM should be considered as a treatment option of comparable efficacy to LHM, albeit with no long-term outcomes data and minimal controlled outcomes data currently available.

From this expert review the following best practices are proposed: 1) in determining the need for achalasia therapy, patient-specific parameters (Chicago Classification subtype, comorbidities, early vs late disease, primary or secondary causes) should be considered along with published efficacy data; 2) given the complexity of this procedure, POEM should be performed by experienced physicians in high-volume centers because an estimated 20−40 procedures are needed to achieve competence; 3) if the expertise is available, POEM should be considered as primary therapy for type III achalasia; 4) if the expertise is available, POEM should be considered as treatment option comparable to laparoscopic Heller myotomy for any of the achalasia syndromes; and 5) post-POEM patients should be considered high risk to develop reflux esophagitis and advised of the management considerations (potential indefinite proton pump inhibitor therapy and/or surveillance endoscopy) of this before undergoing the procedure.

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Conflicts of interest
The authors disclose no conflicts.

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