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New Developments in Esophageal Motility Testing

Rena Yadlapati, MD, MSHS[1,*]
Glenn T. Furuta, MD[2]
Paul Menard-Katcher, MD[1]

Address
[*,1]University of Colorado Reflux & Esophageal Diseases Center, Division of Gastroenterology & Hepatology, Department of Medicine, University of Colorado, Anschutz Medical Campus, Academic Office 1 Room 7605, 12631 E. 17th Ave, Aurora, CO, 80045, USA
Email: Rena.yadlapati@ucdenver.edu
[2]Digestive Health Institute, Children's Hospital Colorado, Aurora, CO; Gastrointestinal Eosinophilic Diseases Program, University of Colorado School of Medicine, Aurora, CO, USA

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Abbreviations *FLIP* Functional luminal imaging probe · *MII-pH* Multichannel intraluminal impedance-pH · *HRM* High-resolution manometry · *EPT* Esophageal pressure topography · *EGJ* Esophagogastric junction · *IRP* Integrated relaxation pressure · *LES* Lower esophageal sphincter · *POEM* Per-oral endoscopy myotomy · *AGA* American Gastroenterological Association · *HRIM* High-resolution impedance manometry · *EII* Esophageal impedance integral · *PPI* Proton pump inhibitor · *EJG-DI* EGJ-distensibility index · *RACs* Repetitive antegrade contractions · *RRCs* Repetitive retrograde contractions · *MNBI* Mean nocturnal baseline impedance · *GERD* Gastroesophageal reflux disease · *PSPW* Post-reflux swallow-induced peristaltic wave

Abstract

Purpose of review The purpose of this review is to present the latest developments in esophageal motility testing and summarize the current paradigm of esophageal motility disorders.
Recent findings While high-resolution esophageal pressure topography interpreted according to the Chicago Classification represents the gold standard to evaluate esophageal motility, recent studies highlight the additional value of novel manometric applications. Novel applications include provocative measures to assess for obstructive physiology at the esophagogastric junction (EGJ), esophageal peristaltic reserve, and rumination and supragastric belching disorders. Furthermore, high-resolution impedance manometry provides assessment of bolus flow in relation to pressure changes. Distinct from manometry, the

endolumenal functional lumen imaging probe examines esophageal motor response to distension to provide complementary and alternative data with regard to EGJ function and esophageal body motor function. Barium esophagram with timed swallow and barium tablet continues to be an important esophageal motility test. Furthermore, current use of multichannel intraluminal impedance-pH monitoring extends beyond reflux monitoring to measure reflux clearance and esophageal epithelial integrity.

Summary The diagnostic armamentarium for esophageal motility disorders has expanded tremendously to include a multitude of sophisticated tools. Advancements in diagnostic technology and understanding of esophageal physiology have shifted the field to more precisely characterize esophageal motility and guide phenotype-driven management.

Introduction

Major diagnostic advances in the twenty-first century have transformed the landscape of esophageal motility disorders. The transition from conventional line tracing manometry to high-resolution esophageal pressure topography plots marks the beginning of a dramatic evolution in esophageal motility. Today, clinicians are equipped with an array of diagnostic tools (i.e., high-resolution impedance manometry (HRIM), endolumenal functional lumen imaging probe (FLIP), and barium esophagram), each with its own distinct applications, to evaluate esophageal motility (Table 1). The rapid expansion of diagnostic technologies over the past 5 years has reframed the understanding of key physiologic concepts such as obstructive esophageal physiology, peristaltic responses to an intraluminal bolus and gastroesophageal reflux, and the function of the anti-reflux barrier. Leveraging these sophisticated tools and the increased appreciation of esophageal physiology, the clinical paradigm has shifted towards utilizing complimentary and novel technologies to guide phenotype-driven treatment for esophageal motility disorders. Therefore, the purpose of this review is to present the latest developments in esophageal motility testing, and summarize the current-day clinical paradigm to evaluate esophageal motility dysfunction.

Developments in esophageal motility diagnostics

High-resolution esophageal pressure topography

The current standard to evaluate non-obstructive esophageal dysphagia is esophageal manometry in the form of high-resolution manometry (HRM) with esophageal pressure topography (EPT). Compared with conventional line tracings, a major advantage of HRM with EPT is the ability to convert pressure tracings into sophisticated and illustrative spatiotemporal plots of esophageal contractility over esophageal length and time, also referred to as Clouse plots in recognition of the visionary Ray Clouse [1]. Along with the evolution of HRM with EPT, another landmark advancement in esophageal motility has been the development of the Chicago Classification, a standardized hierarchical diagnostic classification scheme of esophageal motility disorders, which is currently in version 3.0 [2–5]. These technological and classification advances have transformed what was once considered a complex technology into a more easily understood and interpretable diagnostic tool. In a recent prospective study of 12 physicians, Carlson et al. found superior diagnostic accuracy and inter-rater agreement for HRM with EPT using the Chicago Classification compared to conventional line

Table 1. Applications of current-day diagnostic tools to assess esophageal physiology

Diagnostic Tool	EGJ Obstructive Physiology	Esophageal Peristalsis	Reflux Physiology	Epithelial integrity
HRIM	• IRP • Solid test meal • Rapid drink challenge • Bolus flow time, EII ratio	• Distal contractile integral • Peristaltic reserve with multiple rapid swallow	• EGJ morphology • Post-prandial HRIM	
FLIP	• EGJ distensibility index	• Distension induced contractile response	• EGJ distensibility index	
Barium Esophagram	• Timed swallow • Tablet transit	• Barium transit	• Post-antireflux intervention anatomy	
MII-pH		• Post-reflux swallow peristaltic wave index (PSPWi)	• Acid exposure time • Reflux events (acid/weakly acidic/non-acidic)	• Mean nocturnal baseline impedance
Mucosal impedance				• Direct mucosal impedance

Esophagogastric junction (EGJ), High-resolution impedance manometry (HRIM), Multichannel intraluminal impedance (MII); Functional lumen imaging probe (FLIP); Integrated relaxation pressure (IRP)

tracings and classification scheme across both experienced gastroenterologists and inexperienced gastroenterology trainees [6••]. Despite improved diagnostic interpretation with HRM with EPT, the widespread adoption of HRM across clinical practices exceeds the ability to adequately train and ensure proficiency of interpretation. As such, developing a standardized method to train and assess competency of interpretation is current priority in clinical research [7, 8, 9•, 10, 11].

While the evolution of HRM with EPT and the Chicago Classification represent quintessential advancements in esophageal motility, novel applications of HRM have emerged over the past 5 years and currently play a critical role in the evaluation of esophageal motility. Multiple studies demonstrate that evaluation for obstructive physiology at the esophagogastric junction (EGJ) is imperfect when based solely on the Chicago Classification, and consequently recent studies have focused on identifying other HRM metrics to assess nuanced physiologic properties. For instance, provocation is increasingly used during HRM to evaluate for EGJ obstructive physiology and esophageal peristaltic reserve (Fig. 1). Furthermore, HRM catheters paired with multichannel impedance sensors provide valuable information regarding bolus flow properties. The specific physiologic roles of these novel HRM applications are discussed later in this review.

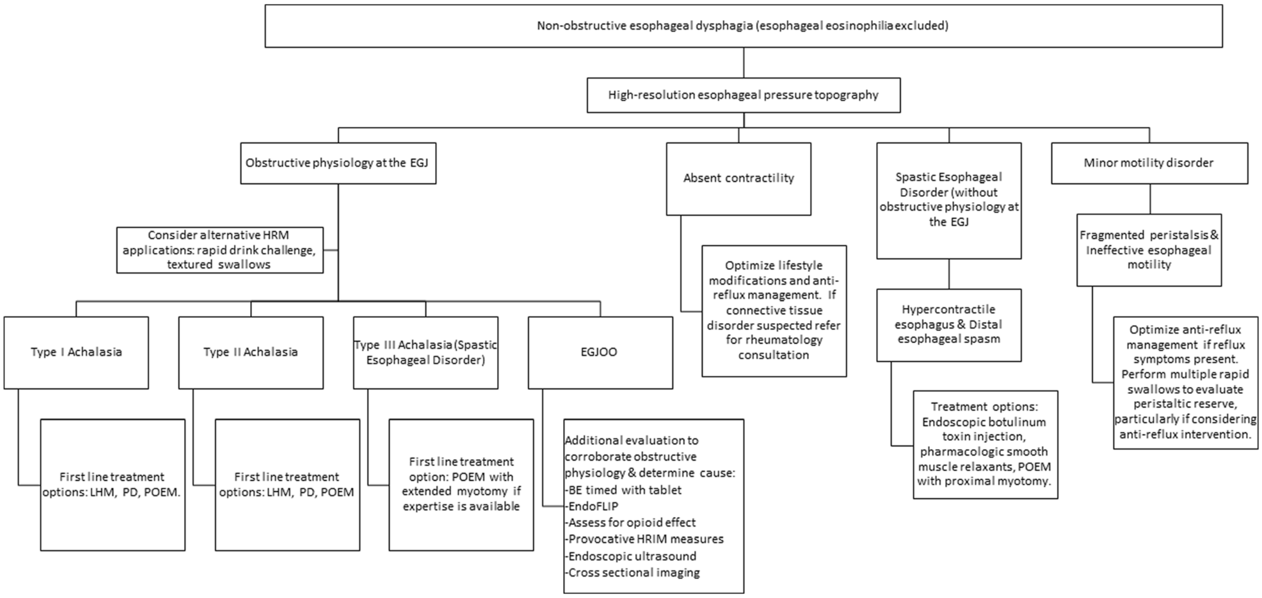

Fig. 1. Current-day clinical approach to the evaluation of non-obstructive esophageal dysphagia

Endolumenal functional lumen imaging probe

The newest diagnostic advancement to assess esophageal motility is the endolumenal functional lumen imaging probe (FLIP). Distinct from esophageal manometry, FLIP leverages high-resolution impedance planimetry during volume-controlled distension to assess esophageal motor responses to distension rather than deglutition. FLIP topography, the most recent version of FLIP, enables real-time topographical assessment of distension-induced esophageal motor characteristics. FLIP assemblies are available in two different balloon sizes: the shorter balloon (EF-325; 8 cm in length) primarily assesses the EGJ, and the longer balloon (EF-322; 16 cm in length) assesses both the EGJ and esophageal body [12••].

Barium esophagram

Prior to widespread adoption of upper endoscopy and esophageal manometry, barium esophagram was the mainstay test to evaluate esophageal motility disorders and gastroesophageal reflux. Today, two applications of barium esophagram remain particularly useful in the evaluation of esophageal motility. Timed barium swallow assesses esophageal emptying of barium sulfate at 1, 2, and 5 min, and has previously been shown to have a prognostic role in predicting symptomatic remission following pneumatic dilation [13]. Barium esophagram with a 13-mm barium tablet is increasingly performed in the evaluation of solid food dysphagia [14••].

Current-day applications of esophageal physiology testing

Esophageal motility serves to transport the oropharyngeal bolus into the stomach and prevent gastroesophageal reflux episodes. Bolus transport is predominantly achieved by primary peristalsis in response to swallowing. Following oropharyngeal transfer of the bolus through a relaxed upper esophageal sphincter, a coordinated esophageal motor response begins and proceeds distally while the lower esophageal sphincter relaxes to accommodate the bolus. Following bolus transit, the lower esophageal sphincter closes with a prolonged contraction to prevent retrograde movement of the bolus into the esophagus. At rest, the lower esophageal sphincter is tonically contracted and overlaps with the crural diaphragm to maintain a high-pressure barrier to gastroesophageal reflux.

Esophagogastric junction obstructive physiology

Historically, the hallmark esophageal motility disorder was achalasia, characterized by abnormal relaxation of the lower esophageal sphincter and absence of esophageal peristalsis. In recent years, the simplistic notion of "achalasia" has significantly evolved to recognize heterogeneous motility patterns presenting with obstructive physiology at the EGJ, each requiring a distinct management approach. Generally, obstruction at the EGJ manifests as dysphagia, regurgitation, and/or chest pain. HRM is the current gold standard to evaluate obstructive esophageal symptoms once a mechanical obstruction, eosinophilic esophagitis, and other inflammatory disorders of the esophagus have been excluded.

EGJ obstructive physiology: HRM

According to the Chicago Classification v3.0, four esophageal motility disorders present with EGJ obstructive physiology, or an elevated median integrated relaxation pressure (IRP). The IRP is a measure of deglutitive relaxation based on 4 s of the lowest mean axial pressure, continuous or discontinuous, across the lower esophageal sphincter. The classic disorder is type I achalasia where 100% of esophageal peristalsis is failed (i.e., distal contractile integral 0 to 100 mmHg-cm-s). Type II achalasia is diagnosed when 100% of esophageal peristalsis is failed and 20% or more of swallows exhibit panesophageal pressurization; type II achalasia is considered to represent a precursor to type I achalasia in disease progression. Type III achalasia is present when 20% or more of swallows exhibit spasticity or prematurity (i.e., distal latency less than 4.5 s), and is akin to spastic achalasia. When criteria for achalasia subtypes are otherwise not met, the diagnosis is esophagogastric junction (EGJ) outflow obstruction [15].

Novel applications of HRM to assess for EGJ obstructive physiology

While the Chicago Classification of esophageal motility disorders relies on the median IRP of ten supine wet swallows to assess EGJ function, recent novel applications of HRM have been described as complementary means to assess for EGJ obstructive physiology (Fig. 1). These methods are particularly useful when the median IRP is borderline and/or the esophageal motor diagnosis per Chicago Classification is incongruent with other diagnostic testing.

Rapid drink challenge

The rapid drink challenge assesses EGJ response to intake of 200 mL of water within 30 s. In 2017, Marin et al. reported that an IRP during a rapid drink challenge of 8 mmHg or greater is indicative of EGJ outflow obstruction, and 12 mmHg or greater is consistent with achalasia [16•]. In the setting of EGJ obstructive physiology, the rapid drink challenge may also incite panesophageal pressurization [17, 18]. When performed with high-resolution impedance manometry (HRIM), bolus height for up to 5 min following a rapid rink challenge can indicate adequacy of bolus clearance [19].

Textured swallows

Bolus consistency influences esophageal motor function. Sweis et al. previously demonstrated that solid swallows performed in an upright position were associated with elevated IRPs [20]. Along these lines, Ang and colleagues found that inclusion of solid swallows in the manometry protocol resulted in an increased diagnostic yield of a major motility disorder [21•]. Therefore, evaluation of EGJ function during textured swallows seems to be particularly useful for patients in whom obstructive physiology is strongly suspected [22].

Bolus flow properties utilizing HRIM

HRM combined with multichannel intraluminal esophageal impedance sensors, referred to as high-resolution impedance manometry (HRIM), provides an enhanced assessment of esophageal motility in relation to bolus flow properties. Since the advent of HRIM, novel metrics to assess bolus retention and EGJ obstructive physiology have been described. The trans-EGJ bolus flow time (BFT) is a novel HRIM application to predict flow across the EGJ. In a study of 60 patients with achalasia and 15 healthy controls, Lin et al. reported a significantly lower median BFT among the achalasia group. Lin and colleagues additionally identified abnormal BFTs in patients with a clinical suspicion of achalasia yet normal median IRP values on HRM [23]. The esophageal impedance integral (EII) ratio is another new HRIM metric to compare the bolus volume during and following the swallow as a measure of bolus retention. In a recent study, the EII ratio distinguished between patients with and without dysphagia despite normal or minor motility motor disorders on HRM [24, 25••, 26••, 27••, 28••]. Thus, HRIM metrics such as the BFT and EII ratio offer sophisticated and complimentary methods to assess bolus flow properties in the evaluation of dysphagia and EGJ outflow obstruction. However, inclusion of these metrics in software analytics and classification algorithms is needed to increase adoption in clinical settings.

EGJ obstructive physiology: FLIP

Distinct from HRM, FLIP evaluates esophageal motor responses to distension rather than deglutition. With regard to EGJ outflow obstructive physiology, FLIP can be used to assess distensibility of the EGJ via the EGJ-distensibility index (EGJ-DI). The EGJ-DI is calculated by dividing the narrowest cross-sectional area through the EGJ over the intra-bag pressure in units of $mmHg^2$ [12••]. Lower EGJ-DI values suggest reduced EGJ distensibility whereas higher EGJ-DI values suggest increased EGJ distensibility [29]. Synthesis of EGJ distensibility and esophageal contractile responses, gleaned from the catheter with the 16-cm balloon (EF-322), can reveal a FLIP topography motility classification. The esophageal contractile response in the setting of a low EGJ-DI can suggest particular subtypes of achalasia or EGJ outflow obstruction. For instance, a low EGJ-DI with an absent contractile response may be similar to an achalasia pattern with absent contractility such as manometric type I or type II achalasia. On the other hand, a low EGJ-DI with the presence of repetitive retrograde contractions (RRCs) may represent a spastic achalasia pattern [30••]. Recent studies examining FLIP also report detection of impaired EGJ relaxation on FLIP not otherwise observed with manometry, and suggest that FLIP may have a complementary and/or alternative role to the gold standard of esophageal manometry in the evaluation of obstructive physiology at the EGJ [31••, 32].

EGJ obstructive physiology: barium esophagram

Barium esophagram continues to play a critical role in the evaluation of obstructive physiology at the EGJ. Blonski et al. recently examined barium esophagram findings among patients with achalasia or EGJ outflow obstruction compared to non-achalasia controls, and identified that a barium column height of 2 cm at 5 min was 85% sensitive and 86% specific for achalasia. Furthermore, combining the timed barium esophagram results with non-passage of a 13-mm barium tablet at 5 min increased the diagnostic yield from 79.5 to 100% [14••]. When assessing for EGJ obstructive physiology, barium esophagram should be considered a complementary diagnostic tool, particularly when the protocol includes timed barium swallow and a barium tablet. Barium esophagram, timed with tablet, is also a reasonable diagnostic alternative if patients are unable to tolerate manometry.

EGJ obstructive physiology: treatment

When EGJ relaxation is impaired with absent contractility (i.e., manometric types I and II achalasia), the treatment goal is to relieve the outflow obstruction across the EGJ. This can be accomplished by laparoscopic Heller myotomy (LHM), pneumatic dilation, or per-oral endoscopy myotomy(POEM). Distinguishing achalasia subtypes has important management and prognostic implications. In the European achalasia trial, combined success rates for LHM or pneumatic dilation for type II achalasia were 96% compared to 81% for type I and 66% for type III achalasia. LHM and PD had similar rates of success in type I achalasia, though the success rate of PD was 100% compared to LHM (93%) in type II achalasia [33]. POEM is the newest treatment option for motility disorders with EGJ obstructive physiology, with reported 90% success rates at 3 years across achalasia subtypes [34•].

While the treatment approaches for achalasia subtypes is well defined, the management for EGJ outflow obstruction remains a challenge. Etiologies of EGJ outflow obstruction vary from an early variant of achalasia, extrinsic vascular obstruction, sliding hiatal hernia, opiate effect, or even a false-positive measurement. Further diagnostic testing to corroborate the obstructive physiology and evaluate for sources of obstruction with cross-sectional imaging, endoscopic ultrasound, barium esophagram with tablet, and/or FLIP are warranted prior to treatment of EGJ outflow obstruction. It is also imperative to attempt opioid discontinuation in the setting of a potential opioid effect [35].

Spastic esophageal disorders

The common feature in spastic esophageal disorders is obstructive esophageal contractility, with or without obstructive physiology at the EGJ. In distal esophageal spasm, the obstructive physiology is a manifestation of premature esophageal contractility (i.e., distal latency less than 4.5 s). Type III, or spastic, achalasia is diagnosed when premature obstructive contractility is paired with obstructive physiology at the EGJ. Obstructive esophageal contractility in hypercontractile, or Jackhammer, esophagus is a result of prolonged and concurrent contractions of the smooth muscle (i.e., distal contractile integral greater than 8000 mmHg-cm-s) which delays the normal post-peristaltic recovery [35]. On FLIP topography, spastic esophageal motility may manifest as three or more consecutively and consistently spaced retrograde contractions, referred to as repetitive retrograde contractions (RRCs) [29].

The current first-line treatment option for type III achalasia is POEM when the expertise is available [36]. A recent meta-analysis of eight uncontrolled observational studies reported a weighted pooled response rate of 92% (95% CI 84–96%) to POEM in type III achalasia with an average extended myotomy length of 17.2 cm [37••]. POEM with extended proximal myotomy is also a treatment option across the other spastic esophageal disorders [37••].

Hypomotile esophageal disorders

Hypomotile esophageal disorders encompass the group of major motility disorders where contractility is entirely absent (i.e., absent contractility) and minor motility disorders. Minor motility disorders are esophageal motility patterns in the setting of a normal median IRP that may be observed in healthy volunteers, and are often seen in gastroesophageal reflux pathology. Manometric minor motility disorders include ineffective esophageal motility, which is diagnosed when 50% or more of swallows are ineffective (i.e., distal contractile integral < 450 mmHg-cm-s), and fragmented peristalsis, which is diagnosed when more than 50% of swallows have breaks longer than 5 cm in the esophageal peristaltic body [5••].

Esophageal peristalsis is the primary innate mechanism to clear gastroesophageal reflux, and over the past 5 years, there has been a growing interest to link metrics of esophageal peristalsis with pathologic gastroesophageal reflux disease. Multichannel intraluminal impedance-pH (MII-pH) is increasingly used to specifically assess post-reflux clearance as well as bolus stasis as a marker of esophageal peristalsis [38, 39]. The post-reflux swallow-induced peristaltic wave (PSPW) index on MII-pH assesses the efficacy of esophageal reflux clearance by measuring the proportion of reflux events that are restored within 30 s. The PSPW index is reportedly lower in erosive and non-erosive reflux compared to controls and patients with functional heartburn [40]. MII-pH also offers the opportunity to examine esophageal impedance as a surrogate of esophageal mucosal integrity and esophageal clearance. The mean nocturnal baseline impedance (MNBI) on MII-pH takes the mean of impedance measurements at three 10-min time periods during the overnight rest period, and is reported to be lower among patients with gastroesophageal reflux disease that respond to anti-reflux measures compared to those who do not [41]. Building on the same concept, direct mucosal impedance was introduced over the past 5 years as a real-time technology performed during endoscopy to assess mucosal integrity. Direct esophageal mucosal impedance during endoscopy has been found to accurately identify patients with erosive esophagitis or positive ambulatory reflux monitoring in multiple studies. Also, mucosal impedance is significantly lower in patients with objective gastroesophageal reflux disease compared to those without, and furthermore, mucosal impedance increases after treatment with PPIs in gastroesophageal reflux disease [42].

Another novel application of HRM as it relates to hypomotile esophageal conditions is the ability to prognosticate risk of post-operative dysphagia following anti-reflux surgery via the multiple rapid swallow. Multiple rapid swallows are administered through five 2-mL swallows taken less than 4 s apart and assess the integrity of deglutitive inhibition and peristaltic reserve. Reduced contractile reserve may indicate gastroesophageal reflux disease at an increased risk of dysphagia following fundoplication [43–45].

Anti-reflux barrier

An additional value of HRM is the ability to assess the anatomy and function of the anti-reflux barrier. With regard to anatomy, HRM examines the spatial relationship between the crural diaphragm and LES, referred to as the EGJ morphology, to assess for hiatal hernia [46]. HRIM is also able to concurrently assess intragastric and intrathoracic pressure in relation to flow of gastric contents, and thereby identifies rumination, belching, and transient lower esophageal sphincter relaxation events. As such, postprandial HRIM is a novel application that monitors symptoms and manometric characteristics following administration of aversive digestive stimuli [47–49]. Postprandial HRIM is increasingly used in the evaluation of nonresponse to proton pump inhibitors (PPIs) to assess for rumination or supragastric belching, and guide phenotype driven management [50].

Conclusion

The evolution of HRM with EPT and the Chicago Classification transformed the field of esophageal motility by not only introducing sophisticated interpretation methods, but moreover generating a new excitement and appreciation for esophageal physiology. Today, the clinical approach to esophageal motility extends far beyond assessing whether EGJ relaxation is adequate with oral intake of water while lying down. In recognition of the fact that the median IRP in a supine position is an imperfect measure of EGJ obstruction, a multitude of alternative methods to assess EGJ function are available such as provocative maneuvers on HRIM, volume-controlled distension of the EGJ using FLIP, and barium esophagram with timed swallow and a barium tablet. An enhanced appreciation of the obstructive physiology in the smooth muscle portion of the esophagus among spastic esophageal disorders enables more precise treatment via proximal myotomy with POEM to effectively alleviate spastic obstructions. Though reflux monitoring and esophageal motility testing were historically distinct diagnostic modalities, today, a multitude of complementary tests (i.e., manometry, MII-pH, and direct mucosal impedance) are used to assess the complex relationship between gastroesophageal reflux physiology, esophageal peristalsis, and epithelial integrity.

Never before have gastroenterologists evaluating patients with suspected esophageal motility disorders found themselves with such a robust armamentarium of diagnostics and nuanced appreciation of physiology. The wealth of information enables gastroenterologists to synthesize sophisticated data points to guide personalized management of esophageal motility disorders. Furthermore, multimodal availability of diagnostic tools offers complementary information in borderline or unclear scenarios. Looking ahead, expanding roles of novel tools performed during upper endoscopy, such as FLIP or mucosal impedance, may with further study obviate the need for more cumbersome testing. In addition, identifying clinically relevant phenotypes of EGJ outflow obstruction will enable precise treatment. Finally, in order to bridge the growth of research findings to optimized patient care, future efforts must focus on patient-centered outcomes, assure competency in diagnostic interpretation, and upgrade software and classification schematics.

Author Contributions

RY, GTF, PMK: literature review, manuscript drafting, and final review.

Compliance with Ethical Standards

Conflict of Interest
Rena Yadlapati is a consultant for Ironwood Pharmaceuticals, Diversatek, and Medtronic, and received grants from NIHNIDDK and the American College of Gastroenterology.
Glenn Furuta reports grants from NIHNIDDK and personal fees from Shire, outside the submitted workIn addition; Dr. Furuta has a patent (EnteroTrack) licensed, and a patent (UpToDate) with royalties paid. Paul Menard-Katcher declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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