Curr Treat Options Gastro (2019) 17:1–17
DOI 10.1007/s11938-019-00213-w

Esophagus (PG Iyer, Section Editor)

Advances in the Diagnosis and Treatment of GERD: New Tricks for an Old Disease

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Published online: 25 January 2019

This article is part of the Topical Collection on *Esophagus*

Keywords GERD · Diagnostics · Treatment · Manometry · Motility · Mucosal impedance testing

Abstract

Purpose of review Gastroesophageal reflux disease (GERD) is a common diagnosis encountered by both primary care providers and specialists, but despite its prevalence, there are limitations in the current diagnostic tests for GERD. Once an accurate diagnosis is made, treatment options can be offered, and this field continues to burgeon with options. In this review, we seek to review the recent advances in GERD diagnostics and subsequent treatment options.

Recent findings Novel impedance markers and novel techniques (mucosal impedance testing, salivary pepsin, high-resolution manometry, and narrow-band imaging) have shown promise in diagnosing GERD. Advances in medical therapy, including potassium-competitive acid blockers and bile acid sequestrants, along with advances in invasive therapy (transoral incisionless fundoplication, endoscopic radiofrequency, electrical stimulation of the LES, and magnetic sphincter augmentation) have provided additional options for therapy for GERD beyond PPI and anti-reflux surgery.

Summary Novel impedance markers and techniques will provide further clarity on mucosal integrity and the barrier function allowing improved diagnostic accuracy of GERD. Improvements in medical and invasive therapy will expand GERD therapy.

Introduction

Gastroesophageal reflux disease (GERD) has a worldwide prevalence (ranging from 8 to 33%) with high burden of cost (upwards of ten billion dollars a year), yet the diagnosis remains elusive leading to over-prescription of anti-reflux therapy and prolonged GERD therapy in the absence of GERD [1, 2]. Etiological factors of GERD include dysfunction of the esophagogastric junction (EGJ), ineffective acid and bolus clearance, increased intragastric pressure, and anatomical changes of the gastroesophageal junction, such as a hiatal hernia, leading to mucosal injury [3, 4]. The current diagnosis of GERD involves endoscopic identification of mucosal injury or identifying troublesome symptoms of typical GERD, which include heartburn and/or regurgitation. More challenging are the symptoms of extraesophageal GERD (hoarseness, cough, and asthma), where empiric trials of high-dose proton pump inhibitors (PPI) are the advocated first-line attempt for symptom relief. Unfortunately, the PPI dose reduction strategy after the initial high-dose trial is often not completed [5–7]. When symptoms improve with a PPI trial, the symptoms are believed secondary to GERD. The endoscopic signs of mucosal injury are primarily determined by the physiology of the EGJ, esophageal peristalsis, and presence of hiatal hernia [8]. These physiological changes have important effects on the anatomical consideration at play in the mucosal injury of GERD. Hence, GERD can be defined by a triumvirate of factors including symptoms, pathology on endoscopy, and physiological changes of the EGJ.

Several diagnostic strategies for GERD exist, and understanding the benefits and the limitations can guide therapeutic interventions for GERD. Moreover, understanding these limitations can help understand when GERD is not the cause of troublesome symptoms to prevent unnecessary anti-reflux medication and surgery. Unfortunately, diagnosing GERD remains a challenge due to poor performance characteristics of currently available diagnostic tests. Optimizing diagnostic tests could reduce the use of suboptimal diagnostic tests and unnecessary cost. In this review, we strive to highlight the challenges of the diagnosis of GERD and how recent advances in GERD evaluation and treatment can help guide future therapy.

Pathophysiology of GERD

The understanding of the pathophysiology of GERD, and subsequently the approach to treatment, has evolved significantly in the last 150 years. In the late 1940s, Phillip Allison proposed hiatal hernia as a major cause of reflux disease, a theory that prevailed for over 20 years [9, 10]. It was not until the 1970s, when manometry began to be utilized more often, that there was a shift towards the theory of lower esophageal sphincter dysfunction in place of hiatal hernias as a major contributor to reflux. The sleeve sensor developed by Dent et al. in 1976 demonstrated that it was not necessarily dysfunction of the LES but the transient relaxation of the LES (TLESRs) that contributed to reflux symptoms [9, 10]. The modern understanding of GERD focuses on the interplay of multiple risk factors. It is the continued improvement of technology and its implementation that has allowed for an overall more complete understanding of this complex disease process.

Advances in diagnostic testing

GERD is often empirically diagnosed and treated by symptom assessment with a PPI trial without invasive testing. Further confirmatory testing is requested when there are persistent symptoms, needed clarity if symptoms are physiologically due to GERD, or to monitor for complications of GERD. Each diagnostic test for GERD has its own limitation in its sensitivity and specificity,

which are important to recognize for the ordering provider. Compared to atypical symptoms of GERD, typical symptoms of GERD are more likely to respond to a PPI trial, in which case a history can provide important distinction of GERD symptoms. Unfortunately, a clinical history has been shown to have a 70% sensitivity and 67% specificity when compared to pH metry or endoscopy [11]. GERD questionnaires have similar operative characteristics as the clinical history owing to the heterogeneity of this disease process presentation and non-GERD symptoms [11, 12]. Often endoscopy is performed when a PPI trial does not help with the presenting symptoms. Endoscopy with biopsy can confirm a diagnosis of GERD if there is Los Angeles Classification Grade C or D esophagitis, Barrett's esophagus, or peptic stricturing; however, in the absence of these findings, the sensitivity of endoscopy falls depending on the degree of esophagitis and the interobserver variability of endoscopic findings [13–17].

When endoscopy is non-confirmatory, the patient has atypical symptoms of GERD, or there is concern for the need for anti-reflux therapy, then ambulatory reflux monitoring can be considered. Wireless pH monitoring is expensive limiting is availability. An alternative choice is pH impedance monitoring, which detects acid and non-acid reflux and is considered the gold standard. The added value of pH impedance over wireless pH monitoring is debated; it is not widely available and can be difficult to interpret [18–20]. Utilizing the information of wireless pH monitoring and pH impedance, reflux symptom associations were created including the symptom index (SI) and symptom association probability (SAP). Unfortunately, these associations are reliant on patient fidelity of associating their symptoms with initiation of the reported events, which has been shown to be limited in its reproducibility. Given this current state of diagnostics, several advances have been made in this field. The following reviews the novel impedance parameters and novel techniques for the diagnosis of GERD (Table 1).

Novel impedance parameters

Postreflex swallow-induced peristaltic wave index

Novel impedance-detected parameters have been developed, which have shown to be clinically significant in differentiating GERD from functional heartburn. Reflux of acidic content into the esophagus results in a natural peristalsis to neutralize this content. The antegrade progression of impedance decline within 30 s of a reflux episode is known as the postreflux swallow-induced peristaltic wave (PSPW) on a pH impedance study, which is lower in GERD as compared to controls. The PSPW index is obtained by dividing the number of PSPWs by the proportion of reflux episodes [21–23]. The PSPW index provides an assessment of the integrity of primary peristalsis stimulated by reflux episodes and correlates with contraction reserve assessed using multiple rapid swallows. The PSPW index has shown excellent operative characteristics with a sensitivity of 99–100% and specificity of 92% for differentiating GERD from functional heartburn [21, 24, 25•]. There are several limitations of the PSPW index, which include that it is not programmed into the current software and is cumbersome to calculate which has limited is distribution of use to research purposes. Moreover, it involves catheter-based ambulatory testing, which is uncomfortable and prolonged.

Table 1. Comparison of novel diagnosis of GERD

	Methods	Advantages	Disadvantages
Novel index	1. PSPW 2. Mean nocturnal baseline impedance	1. Decreased in esophagitis, NERD, Barrett's esophagus, and EoE 2. Normal in functional heartburn	1. Requires catheter-based pH impedance 2. Requires manometry 3. Uncomfortable for patients 4. Uncertainty that impedance electrodes in contact with esophageal epithelium 5. Requires extensive calculations (research only) 6. Needs further validation
Novel techniques	1. Mucosal impedance testing	1. Decreased in esophagitis 2. Data acquisition in short period, eliminating needs for ambulatory testing 3. Can measure MIT values along esophageal axis and radial distribution 4. Normal in health individuals and functional heartburn	1. Requires endoscopy 2. Liquid and air esophagus may confound the results 3. Cost unknown 4. Pending validation studies
	2. Salivary pepsin	1. Non-invasive 2. Detected in high proportion of patients with GERD	1. Requires validation 2. Low sensitivity
	3. High-resolution manometry	1. Can detect alternative major motordisorders prior to anti-reflux surgery or when symptoms do not improve with GERD therapy. 2. EGJ-CI identifies a subset of patients with severe barrier dysfunction prone to either endoscopic esophagitis or unequivocally abnormal reflux testing	1. No single metric adequately summarizes EGJ competence 2. Validation studies needed
	4. Narrow-band imaging	1. Distinguishes normal from NERD and reflux esophagitis 2. Correlates with esophagits and rules out EoE	1. Not readily available at all centers 2. Needs validation studies on response to therapy

Mean nocturnal baseline impedance

In addition to the PSPW index, baseline impedance can be obtained, which has shown to be a sign of mucosal integrity via changes in intracellular spaces and tight junctions. In healthy esophageal epithelium, tight junctions prevent a permeable mucosa, which gets disrupted by gastric acid, bile acids, and pepsin leading to mucosal injury and permeability [26–31]. One surrogate impedance marker is the mean nocturnal baseline impedance (MNBI), which uses impedance values while asleep when averaged from three 10-min periods spaced an hour apart. Obtaining values at night can help prevent daytime variation of values, which is affected by frequent swallows [32]. Lower MNBI values have been shown to help distinguish persistent esophagitis from healed esophagitis, PPI-responsive chronic cough and NERD compared to non-responsive PPI cough and NERD, and in GERD/NERD compared to functional heartburn and health controls [22, 23, 33]. Furthermore, low MNBI values predict successful response to surgery, and MNBI values improve with healing of esophagitis showing the dynamic feature of this test [34–36]. Both the PSPW index and MNBI provide diagnostic advantage in classifying patients as hypersensitive esophagus when both of these impedance values are abnormal despite normal acid exposure time and negative SI and SAP [37]. The limitations of the MNBI values are similar to the PSPW index in that it is cumbersome to calculate and involves and uncomfortable catheter in the ambulatory setting for a prolonged amount of time.

Novel techniques

Mucosal impedance testing

Mucosal impedance testing (MIT) is obtained in real time and has been developed to assess mucosal changes to diagnose GERD without the need for prolonged ambulatory monitoring. MIT is obtained using a catheter that goes through the working channel of the endoscopy which has two radial sensors mounted on a 10-cm balloon that is inflated allowing long segment of esophageal mucosa. Measurements are taken over a 10–15-s period during endoscopy preventing the need for prolonged and cumbersome ambulatory pH or impedance monitoring. MIT values have been shown to differentiate erosive and non-erosive GERD from eosinophilic esophagitis and normal patients with improved operative characteristics when compared to pH monitoring (specificity of 95% vs. 64% and positive predictive value of 96% vs. 40%) [38, 39]. Similar to MNBI, MIT values normalize following PPI therapy in patient with GERD. In contrast to MNBI which uses night-time impedance values, MIT is obtained at the time of endoscopy with no need for prolonged monitoring allowing for real-time data collection and analysis [40]. Inflammatory conditions of the esophagus, such as eosinophilic esophagitis (EoE), also lead to lower mucosal impedance, and this technology has been shown to help detect EoE expanding on its application of esophageal mucosal integrity [41–43]. Outcome studies are still needed to determine if MIT can predict response to PPI or surgery, which limits its ability to be the definitive tool for diagnosis of GERD [6].

Esophageal high-resolution manometry

High-resolution manometry (HRM) is performed to confirm placement of impedance catheter and to evaluate for other major motor disorders prior to anti-reflux surgery when symptoms of GERD do not respond to PPI therapy. HRM is often completed in the setting of reflux, and evaluation of the incompetence of the EGJ has been studied given his anti-reflux barrier property. The EGJ is a complex structure composed of the crural diaphragm (CD) and lower esophageal sphincter (LES) which changes with respiration and swallowing [44]. The Lyon Consensus aimed to characterize EGJ competency using two markers: EGJ morphology and EGJ contractile integration [45•]. The first marker involves defining EGJ morphology into three categories of the interaction of CD and LES. In this EGJ morphology nomenclature, type 1 has superimposed LES and CD, type 2 with axially separated LES and CD pressure signals separated by < 3 cm, and type 3 with a ≥ 3-cm separation between the LES and CD pressure signatures. The second marker is the EGJ contractile integral (EGJ-CI), which involves not only calculating the distal contractile integral (DCI) but also encompassing the LES and CD. This DCI box equivalent is calculated over a period of three respiratory cycles above a threshold of gastric pressure, which is then divided by the duration time of these respiration cycles. This metric has been shown to allow distinction for those patients with GERD who will develop esophagitis or will have abnormal reflux testing. Though these values require invasive impedance monitoring, they can he helpful in the diagnoses of GERD [46–51].

Salivary pepsin measurement

Salivary pepsin-level measurement has been proposed as a way to diagnose GERD [52]. Gastric chief cells release pepsinogen which is a precursor to the proteolytic enzyme pepsin. In a study with 58 patients with GERD (diagnosed by esophagitis and/or abnormal pH) compared to 51 controls, salivary pepsin test performed with an 81% positive predictive value and a 78% negative predictive value [53]. Immunological assays perform better than enzymatic assays, which can vary with conditions and are difficult to standardize. Salivary pepsin measurements have compared well against pH metry or pH impedance monitoring. Given the non-invasive nature of this test, it would be ideal for the diagnosis of pediatric GERD or extraesophageal reflux. Unfortunately, current data is inconclusive or negative in these subgroups [54, 55]. Current limitations of this test are in part due to lack of standardization sampling protocols and change of reference normal values from manufacturers leading to difficulty in accurate data collection. Moreover, only 45–50% patients with known reflux have positive salivary pepsin positive results. Once protocols are standardized, a multi-center approach is needed to replicate the current data in typical GERD patients prior to clinical use.

Narrow-band imaging

Narrow-band imaging (NBI) uses a spectral narrow-band filter to help detect mucosal pattern changes due to histological changes. NBI increases the contrast to allow microvasculature changes and has improved reproducibility of grading esophagitis [56, 57]. In one study comparing standard white-light endoscopy to

NBI, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in predicting therapeutic response were 33.8%, 100%, 100%, 28.3%, and 47.6% for standard endoscopy; 52.3%, 88.2%, 94.4%, 32.6%, and 59.8%, for narrow band imaging; and 70.8%, 64.7%, 88.4%, 36.6%, and 69.5%, for narrow band imaging with magnification [58]. Given its cost, it is not a first-line method of diagnosis, but can be used as an adjunct for diagnosis.

Advanced in treatment: medical

The importance of diagnostic testing cannot be understated as treatment options are dependent on a correct diagnosis. A PPI trial is often both a diagnostic and therapeutic test, and PPIs have become standard care for GERD treatment. However, symptoms may still be present in approximately 40% of patients [59]. Furthermore, symptom control can vary from 56 to 77% of patients with erosive esophagitis and 37–61% with non-erosive esophagitis [60••]. The following reviews the advances in medical and invasive therapy for GERD (Table 2).

CYP2C19 polymorphisms

One consideration when facing a patient with PPI non-responsive symptoms is to consider switching to a PPI that is not dependent on CYP2C19 for metabolism [59]. Polymorphisms in the CYP2C19 result in three distinct phenotypes with different metabolization capabilities: the extensive metabolizers, the poor metabolizers, and those in between (the heterozygotes) [59]. One meta-analysis found that extensive metabolizers with erosive esophagitis have lower response rates to CYP2C19-dependent PPIs (such as omeprazole and lansoprazole) as compared to heterozygotes or poor metabolizers [59]. Response rates, however, were much more similar in studies comparing these three metabolizer groups when the more CYP2C19-independent PPIs (rabeprazole and esomeprazole) were used. In the meta-analysis, only a few included a direct comparison of both CYP2C19 dependent and independent PPIs; the conclusions at least suggest a wider role of the more CYP2C19-independent PPIs in the treatment of GERD patients with refractory symptoms [59].

Potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs) are a new, promising class of medications that are being evaluated for their effectiveness in treating GERD. These medications work by competing for potassium ions at the proton pump, thus reversibly inhibiting its function [60••, 72]. Vonoprazan is the first clinically available P-CAB (released in Japan in 2015) approved for the treatment of GERD, though it is not currently available in the USA [60••, 72]. Compared to PPIs, Vonoprazan has been shown to have faster onset and suppresses acid secretion for a longer period of time [60••, 72]. It is also not metabolized by the CYP2C19 enzyme, thus avoiding some of the limitations of PPIs [61, 72]. When compared to lansoprazole in the healing of erosive esophagitis at 8 weeks, Vonoprazan was found to be non-inferior (99% effective compared to 95.5%

Table 2. Therapeutic advances in GERD

	Therapy	Pros	Cons	Evidence	Number analyzed	Endpoints of trials	References
Medications	Potassium-competitive acid blockers (P-CABs)	- Fast onset - Long lasting - No major short-term side effects - Not dependent on CYP2C19 metabolism to work	- Unclear how well GERD symptoms controlled - Not currently available in the USA - Associated with higher levels of gastrin in humans and higher rates of neuroendocrine tumors in mice	1. Randomized, double-blind study 2. Multi-center, randomized, double-blind study	1. 19 patents on PPIs with endoscopically confirmed erosive esophagitis (EE) 2. 401 patients with endoscopically confirmed EE	1. Time gastric and esophageal pH > 4 and percentage of EE healing at 8 weeks; P-CAB use significantly increased percentage of time gastric pH > 4 and also had a > 60% EE healing rate 2. Percentage of patients with healed EE in PPI group vs. P-CAB group, confirmed by endoscopy; study demonstrated non-inferiority of P-CABs	[61, 62]
	IW-3718	- Appears to reduce symptoms of heartburn/ regurgitation compared to placebo in patients with PPI refractory disease	- Awaiting phase 2B and phase 3 study results	1. Phase 2A randomized, double-blind placebo-controlled study 2. Double-blind placebo-controlled study	1. 93 patients with GERD on PPIs and still symptomatic 2. 280 patients with erosive esophagitis ± abnormal pH study, on PPIs and still symptomatic	1. Heartburn-free days increased in patients receiving IW-3718 vs. placebo 2. Greater decrease in heartburn severity score over 8 weeks in the IW-3718 groups vs. placebo (dose-response)	[63]
Endoscopic therapies	Endoscopic radiofrequency	- Some evidence to support improved quality of life, reduced heartburn symptoms, reduced PPI use, and reduced erosive esophagitis - Safe procedure	- Conflicting evidence among different studies	1. Meta-analysis of randomized control trials only 2. Meta-analysis of randomized and cohort studies	1. 153 patients across 4 RCTs 2. 2468 patients across 28 total studies (4 RCTs, 23 cohorts, and 1 registry)	1. Efficacy of radiofrequency (RFA) compared to sham or PPI; no difference seen in time pH > 4, ability to stop PPIs, health-related quality of life (HRQOL), or LES pressure 2. Efficacy of RFA in treating GERD; significant improvement in HRQOL and heartburn score, decreased PPI use, EE incidence, and esophageal acid exposure, but no increased LES pressure	[64, 65]

Table 2. (Continued)

	Therapy	Pros	Cons	Evidence	Number analyzed	Endpoints of trials	References
	Transoral incisionless fundoplication (TIF)	- Some data supporting improvement in HRQOL scores compared to other treatment options. - Minimally invasive	- Risk of perforation, bleeding, pneumothorax - Effects do not seem to last over time	1. Meta-analysis 2017 2. Meta-analysis 2018	1. 963 patients across 18 studies (all RCTs or prospective observational studies) 2. 1128 patient across 7 trials	1. Efficacy of TIF compared to PPI or sham; total episodes of refluxes decreased in TIF group, however, no difference in amount of time esophagus exposed to acid or number of acid refluxes compared to PPIs 2. Efficacy of TIF compared to PPI or laparoscopic Nissen fundoplication (LNF); only scores for HRQOL improved in the TIF group. TIF was less effective in increasing LES pressure and in decreasing time pH < 4 compared to LNF.	[66, 67]
Surgical options	Electrical stimulation of LES	- Significant decrease in acid exposure and improvement in HRQOL - Decrease in PPI use - Few significant side effects	- Small studies with short follow-up so far - Awaiting results from ongoing controlled trials - Possibility, though rare, of organ damage from misplaced LES lead or lead erosion	1. Open-label, single-center study 2. Prospective, open-label, uncontrolled multi-center study	1. 23 patients with esophagitis and partial response of symptoms to PPI 2. 41 patients with partial response to PPI	1. Safety and efficacy of procedure at 12 months; no adverse events + improvement in HRQOL and esophageal acid exposure, as well as decreased PPI use 2. Safety and efficacy of procedure at 6 months; 1 device-related and 1 procedure-related serious adverse events + improvement in HRQOL and esophageal acid exposure	[68, 69]
	Magnetic sphincter augmentation (MSA)	- Decreased need for BID PPI dosing escalation - Minimally invasive	- Dysphagia, reflux, chest pain, D11, and vomiting which required removal of MAS; dysphagia improved with removal, but vomiting did not improve after removal	1. RCT 2018 2. Prospective Trial 2016	1. 152 GERD patients > 21 years with moderate-to-severe regurgitation despite 8 weeks of once-daily PPI therapy were prospectively enrolled 2. 100 adults with GERD for 6 months or more, who were partially responsive to daily	1. Efficacy of TIF compared to PPI or sham; total episodes of refluxes decreased in TIF group, however, no difference in amount of time esophagus exposed to acid or number of acid refluxes compared to PPIs	[70, 71••]

Table 2. (Continued)

Therapy	Pros	Cons	Evidence	Number analyzed	Endpoints of trials	References
				proton pump inhibitors (PPIs) and had evidence of pathologic esophageal acid exposure, at 14 centers in the USA and The Netherlands	2. All patients used PPIs at baseline; this value decreased to 15.3% at 5 years. At baseline, the median GERD-HRQL scores were 27 in patients not taking PPIs and 11 in patients on PPIs; 5 years after device placement this score decreased to 4	

for lansoprazole) [60••, 61, 72]. Among patients with the most severe esophagitis (LA-C/D), Vonoprazan was actually significantly more likely to heal esophagitis than lansoprazole (98.7% vs. 87.5%) after 8 weeks. Moreover, the safety profile of Vonoprazan is very similar to that of PPIs, with no major adverse effects being reported in trials to date. Long-term effects are less clear, especially given much higher levels of gastrin in patients treated with Vonoprazan (shown to be associated with higher rates of gastric neuroendocrine tumors in mice) [72]. A randomized, double-blind study examined the effects of P-CAB administration in 19 patients with endoscopically confirmed erosive esophagitis after taking PPIs [62]. This study showed that P-CABs significantly increased the percentage of time that the gastric pH was greater than 4 and also had a > 60% healing rate of PPI-resistant erosive esophagitis at 8 weeks [62]. Longitudinal and comparative studies against PPIs are needed to help determine efficacy.

IW-3718

IW-3718 is a novel therapy being studied to evaluate whether it can reduce ongoing GERD symptoms in PPI users [60••]. IW-3718 is a bile acid sequestrant that remains in the stomach and binds bile in the refluxate [60••, 63]. In a randomized, double-blind, placebo-controlled study with continued PPI use, IW-3718 increased heartburn-free days by 30.3% compared to 24.7% in the placebo group [60••]. Recent data comparing IW-3718 to placebo in the reduction of heartburn and regurgitation symptoms among patients still having significant symptoms on standard dose PPI [63]. There was a 52.9% response rate in heartburn symptoms among subjects taking IW-3718 compared to 37.1% in the placebo group. Similarly, there was also a significant difference in the response rate of regurgitation symptoms among the subjects taking IW-3718 (46.3%) and placebo (34.3%) [63]. Though these are early studies, they do suggest that IW-3718 may be a useful adjunct medication in patients whose GERD symptoms are not well controlled on PPI alone.

Advances in treatment: procedural

In regard to endoscopic innovations in the treatment of GERD, multiple procedures have been developed in recent years, including transoral incisionless fundoplication (TIF), endoscopic radiofrequency, electrical stimulation of the LES, and magnetic sphincter augmentation (MSA).

Transoral incisionless fundoplication

A meta-analysis published in 2017 looked at studies comparing TIF to PPI/sham [66]. TIF was found to decrease the total number of reflux events in comparison to PPIs/sham. The overall response rate (defined as at least a 50% improvement in a GERD quality-of-life measure or complete symptom remission) was also found to be higher in TIF compared to PPI/sham. Esophageal acid exposure time was essentially the same in the TIF group compared to PPIs, but decreased in comparison to sham. However, the effects seen in the group

undergoing TIF decreased with resumption of PPIs postprocedurally (though typically at lower doses than prior to TIF). Another meta-analysis in 2018 compared the efficacy of TIF or PPI to laparoscopic Nissen fundoplication (LNF), which is the gold standard procedure for GERD treatment [67]. Though scores for health-related quality of life in the TIF group improved, LNF was more effective in increasing the LES pressure and in decreasing the amount of time the esophagus was exposed to pH < 4 [67]. A major limitation in the analysis is the lack of direct comparison of TIF to LNF [67].

Endoscopic radiofrequency

Another new endoscopic technique involves the application of radiofrequency to the LES (patented as Stretta), which leads to thickening of the LES and decreases TLESRs and esophageal exposure to acid [60••, 64]. In a meta-analysis of 28 studies, Stretta was found to significantly improve quality of life, reduce heartburn symptoms, reduce PPI use (from 97.1 to 49%), reduce esophageal exposure to acid, and reduce erosive esophagitis incidence (by 24%) compared to baseline [64]. Though the results are promising and almost 2500 patients were included in the meta-analysis, only four of the 28 studies were randomized control trials. There was no comparison to the efficacy of another procedure, such as laparoscopic Nissen fundoplication. In a smaller meta-analysis looking only at four randomized control studies (total of 153 patients), the efficacy of Stretta was compared to that of sham or PPI. This study had a very different outcome, with no difference seen in time, pH was less than four, the ability to discontinue PPIs, health-related quality of life (HRQOL), or LES pressure [65].

Electrical stimulation of LES

Electrical stimulation of the LES, where electrical implants are placed laparoscopically in the muscles at the GE junction, is also being used to treat GERD [60••, 73]. Preliminary studies revealed that LES pressure increased with electrical stimulation [73]. An open-label, single-center study with 25 subjects showed significant decreases in acid exposure and symptoms of heartburn and regurgitation, as well as increases in GERD health-related quality-of-life metrics [73]. Of the 23 patients still available for evaluation 1 year postimplantation, only one subject was still on PPIs and none of the patients had gastrointestinal side effects. Fifteen patients followed up after another 2 years and had improved quality-of-life metrics and decreased exposure to acid compared to baseline [68, 73]. One multi-center study showed similar results, with significant improvement in esophageal acid exposure and health-related quality of life at 6 months [69].

Magnetic sphincter augmentation

MSA, which includes the LINX device, is placed surgically where small flexible band of interlinked titanium beads with magnetic cores is placed surrounding the LES. The magnetic attraction allows accommodation of food bolus into the stomach by temporarily breaking the magnetic bond, but closes after food bolus passage to prevent against reflux. MSA does not require any alteration to the stomach. Prospective trials have been completed to evaluate safety and efficacy. In a prospective,

international study evaluating 100 adults with GERD for 6 months or more, who were partially responsive to daily PPIs and had evidence of pathologic esophageal acid exposure, MSA was evaluated after 5 years [70]. MSA showed improvement in median GERD-HRQL (scores were 27 in patients not taking PPIs and 11 in patients on PPIs; 5 years after device placement, this score decreased to 4), and all patients used PPIs at baseline, which decreased to 15.3% at 5 years [70]. Safety profile at 5 years showed symptoms of dysphagia, chest pain, persistent reflux, and vomiting which required removal of MSA; all symptoms improved with either removal of device of subsequent Nissen fundoplication, except for vomiting which persisted. In a recent randomized control study comparing MSA versus increased PPI from once a day to twice a day, 152 GERD patients >21 years with moderate-to-severe regurgitation despite 8 weeks of once-daily PPI therapy were prospectively enrolled [71••]. Of these patients, 89% (42/47) of treated with MSA has improved of regurgitation as compared to 10% (10/101) of the BID PPI group ($p < 0.001$) at the 6-month primary endpoint [71••].

Conclusion

Despite GERD being a common disease, suboptimal diagnostic tests have made this an elusive diagnosis, especially when symptoms are refractory to PPI or involve pediatric GERD/extraesophageal GERD. Improvements of impedance parameters can be helpful in certain GERD phenotypes, but the cumbersome calculation makes its real-world application limited. Advances in device technology show promise, especially with MIT, but outcome data confirming response to PPI or anti-reflux surgery limits these techniques in their applicability. As the growing concern for reducing PPI dependence for GERD therapy, alternatives to PPI continue to be explored. Understanding the limitations of the PPI and genetic polymorphisms are important considerations. Novel therapies such as Vonoprazan and IW-3718 have been developed to treat GERD and spare PPI usage. Invasive techniques, such as TIF, Stretta, electrical stimulation of the LES, and MSA provide opportunities to better exploit the physiology of GERD to work on therapeutic improvements. As with the diagnostic tests, long-term outcome data compared to both PPI and anti-reflux surgery is needed to determine safety profile, clinical efficacy, and improvement over the current standard of care. Understanding the different phenotype of GERD (erosive reflux disease, non-erosive reflux disease, hypersensitivity esophagus, and functional heartburn) will help define the roles of these novel diagnostic tools and provide information on clinical outcome for therapy.

Author contributions

Authored first draft (RDN, LE), critical revisions (all), approved final draft (all).

Compliance with Ethical Standards

Conflict of Interest
Rishi Naik declares that he has no conflict of interest. Lauren Evers declares that she has no conflict of interest. Michael Vaezi declares that he has 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.

Financial and Competing Interest Disclosure
Competing interest:
Vanderbilt and Diversatek co-own the patent on MIT technology discussed in this review.
No writing assistance was utilized in the production of this manuscript.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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