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Review Article

Current advances in the diagnosis and management of gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is very common and defined as troublesome symptoms owing to excessive acid reflux. The spectrum of GERD is broad, including not only erosive esophagitis and Barrett's esophagus but also nonerosive reflux disease (NERD), reflux hypersensitivity, and functional heartburn. Patients with reflux symptoms despite normal endoscopy remain common clinical presentation, can be heterogeneous overlapping with functional gastrointestinal disorders. Ambulatory esophageal pH monitoring with and without impedance helps the diagnosis of NERD. Metrics such as baseline impedance and postreflux swallow induced peristaltic wave enhance diagnostic accuracy in patients with inconclusive diagnoses. The major treatment of all manifestations of GERD is acid suppression with proton pump inhibitors, while other therapies, such as reflux-reducing agents and adjunctive medications, can be individualized where the response to traditional management is incomplete. GERD patients often need long-term treatment due to frequent relapses. Anti-reflux surgery can be effective too. Endoscopic therapies have some promising results, but long-term outcomes remain to be determined.

Keywords: *Gastroesophageal reflux disease, Impedance-pH, Proton pump inhibitors*

Introduction

Gastroesophageal reflux disease (GERD) is the result of reflux of gastric contents entering into the esophagus in sufficient quantities to cause troublesome esophageal and/or extra-esophageal symptoms, with or without mucosal erosions and/or relevant complications (peptic stricture, esophageal ulceration, Barrett's esophagus, esophageal adenocarcinoma) [1]. The typical symptoms of GERD are recognized as heartburn and regurgitation. Extra-esophageal symptoms are broad and heterogeneous and are variably in literature as laryngeal, oropharyngeal, pulmonary, and cardiac. This range in presenting phenotypes demonstrates the profound effects of GERD on other organs, most in the proximity to the esophagus [1,2]. GERD is a common disorder with its prevalence, as defined by at least weekly heartburn and/or acid regurgitation, estimated to range from 10% to 20% in Western countries. Although similar rates are <5% in Asian countries [3], it has been demonstrated that GERD is emerging as a leading digestive disorder in Asian countries [4]. GERD can impact on quality of life [5], and has been reported that the majority of patients with typical reflux symptoms have negative endoscope [6]. However, some patients with esophageal erosions did not experience any symptoms [7]. In addition, atypical symptoms including cough, chest pain, and globus sensation appear to be quite prevalent in patients with GERD (20%–0%) [8]. Notably, atypical symptoms are more often reported in individuals ultimately found to have nonerosive reflux disease (NERD) [1].

Considerable developments emphasizing the importance of optimized management in patients with GERD have emerged

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in recent years. It has been observed that the absence of erosive esophagitis is common in community-based practices [9]. In addition, those patients have a less favorable response to proton pump inhibitors (PPIs) as compared to those having erosive esophagitis [10]. The Rome IV Committee recently outlined the classification scheme for functional esophageal disorders including reflex hypersensitivity and functional heartburn, based on typical GERD symptoms with normal acid exposure time in individuals considered not responsive to PPIs [11].

Pathophysiology

Impaired esophagogastric junction barrier

An ineffective esophagogastric junction (EGJ) barrier is consistently present in GERD, often combined with morphological abnormality (hiatus hernia). Transient lower esophageal sphincter relaxation (TLESR) is a physiological response to gastric distension, and excessive reflux during TLESRs is the most common EGJ event seen in patients with GERD [12]. An intact EGJ should be composed of a lower esophageal sphincter and diaphragmatic crura. An impaired EGJ barrier can be hypotensive lower esophageal sphincter that can be overcome by increased intra-abdominal pressure or disrupted and separated lower esophageal sphincter and diaphragmatic crura (hiatus hernia), or both. In patients with hiatus hernia, the resting tone of the intrinsic lower esophageal sphincter is typically hypotensive, with esophageal reflux burden higher under these circumstances than with either abnormality alone [13]. Consequently, both types of EGJ abnormalities can coexist and both can result in abnormal reflux burden.

Esophageal hypomotility

When a reflux episode occurs, the refluxate can be cleared by a combination of a secondary peristaltic contraction and a primary post-reflux swallow-induced peristaltic contraction that also brings saliva to neutralize esophageal mucosal acidification [14]. In many patients with GERD, esophageal motor function is intact and normal [15]; however, hypomotility can contribute to delayed esophageal clearance and increases the likelihood of esophagitis [16]. More severe GERD was found in patients with more ineffective swallows [17].

Refluxate and acid burden

The gastric acid forms a layer of acid floating on the top of ingested food just below EGJ, the acid pocket [18]. In patients with hiatus hernia, the acid pocket can move into the distal esophagus, causing prolonged acid exposure in the distal esophagus [19]. Delayed gastric emptying and acid hypersecretory states, such as in gastrin-secreting tumors (gastrinomas), are additional predisposing factors that contribute to esophageal reflux burden [12]. Acid and other components of the refluxate (pepsin, bile acid) can participate in mucosal damage and complications including Barrett's esophagus [20]. Patients with reflux hypersensitivity or functional heartburn report similar symptoms to typical GERD, potentially through peripheral and central mechanisms, despite reflux burden being regarded as physiological level [11,21].

Psychiatric comorbidity and hypervigilance

Psychosocial comorbidities can influence the symptom presentation and therapeutic response of GERD [22]. Esophageal hypervigilance is a neurological process of both cognition and mood, such as increased attention to esophageal sensations or stress about GERD symptoms [22]. Recently, the esophageal hypervigilance and anxiety scale (EHAS) has been proposed as a validated cognitive-affective evaluation of centrally mediated esophageal symptom perception, and positively correlates with symptom severity of GERD, but is not influenced by 24-hour impedance-pH metrics including acid reflux burden, number of reflux events or mucosal integrity [23,24]. Thus, EHAS is a measure of patient perception of symptoms, it provides insights into psychological modifiers of symptom perception, and could be an important metric to assess outcome of GERD therapy independent of the modality [24].

Diagnostic testing for gastroesophageal reflux disease

A diagnosis of GERD is often clinically made based on typical symptoms and the response to PPIs [25]. There are generally two main approaches for the diagnostic test: Endoscopic confirmation of esophageal mucosal injury, and catheter detection of pathologic acid exposure by prolonged ambulatory monitoring with pH or combined pH-impedance [26].

High resolution manometry

Although high-resolution manometry (HRM) is not used for the diagnosis of GERD itself, patients with GERD often have abnormal esophageal motility [17]. A recent study utilizing HRM revealed that acid reflux burden is more profound in patients with absent primary peristalsis, as well as in patients lacking a secondary peristaltic response to esophageal air distension [27]. HRM is recommended to exclude diagnosis other than GERD in patients with esophageal symptoms and failed PPI treatment. Achalasia can present with typical reflux symptoms together with dysphagia [28].

Endoscopy

The Los Angeles (LA) classification is the most common grading system of reflux-related esophageal injury, including mild (grades A and B) and severe (grades C and D) esophagitis [29]. However, about two-thirds of untreated patients with heartburn and regurgitation do not have erosive esophagitis, absence of esophagitis does not rule out GERD [30]. Since endoscopists have significant variability in determining mild erosive esophagitis [31], pH-metry test is recommended to document GERD in patients with mild erosive esophagitis before anti-reflux surgery [32]. Furthermore, biopsies should be done if eosinophilic esophagitis or Barrett's esophagus is suspected.

Reflux monitoring

The main purpose of reflux monitoring is to document whether a pathologic level of reflux is present. Reflux monitoring can record the correlation of symptom and

reflux. Reflux monitoring is performed either by pH-metry or pH-metry combined with impedance.

Catheter-based and wireless pH monitoring

Ambulatory pH monitoring records in the distal esophagus. Transnasal catheter record over a 24–h period and wireless pH capsule can record up to 96 h. Parameters derived include acid exposure time (time percentage of esophageal pH <4 over the total time), reflux episode number, prolonged reflux episode number (reflux episode >5 min), and longest reflux episode. All these parameters can be combined in a composite score, DeMeester score [33]. A positive pH test establishes a diagnosis of GERD when even the endoscopy does not reveal evidence of erosive esophagitis. A positive pH test can also confirm or exclude GERD in patients who do not have adequate symptom control with a PPI. An abnormal 24–hour pH score was associated with successful outcome of laparoscopic fundoplication (odds ratio of 5.4; 95% confidence interval, 1.9–15.3) [34]. Wireless pH monitoring is more tolerated for prolonged recording, and has similarly accuracy compared with catheter-based pH monitoring [35]. The definitions of NERD, acid hypersensitive esophagus and functional heartburn rely on the interpretations of the temporal relationships between symptoms and reflux events assessed with symptom index (SI), symptom association probability (SAP) or both. SI is a simple, easy to determine and understand parameter, and describes the proportion of symptoms that are reflux-related. SAP describes the probability that the observed relation between symptoms and reflux does not occur by chance. The analysis of symptom-reflux association is still clinically helpful to better identify those patients with symptoms that are related to acid reflux.

Impedance-pH monitoring

Standard pH monitoring allows measuring acid reflux by detecting pH drops in the distal esophagus. However, when gastric acid was buffered in the postprandial period or suppressed by a PPI, refluxate can become pH >4, which is weakly acidic reflux or nonacid reflux. In addition to pH monitoring, impedance-pH monitoring characterizes fluid and gas as well as detects the movement of fluid and gas. Combined pH and impedance recording technology enable the detection of acid and nonacid reflux episodes. This technology also allows for better characterization of the proximal extent of reflux, postreflux clearance, reflux episodes, including not only acidity (acid, nonacid) but also composition (air, liquid, or mixed). Therefore, it is currently considered to be the most accurate and detailed method to assess gastroesophageal reflux [36]. Adding impedance to pH monitoring improves the diagnostic yield and allows better symptom analysis. Several studies have evaluated the use of 24–h pH-impedance monitoring in refractory patients taking PPIs twice daily, and the results can be summarized as follows: 50%–60% of patients do not have symptoms that can be associated with GERD, 30%–40% have symptoms associated with nonacid reflux, and approximately 10% have symptoms associated with acid reflux [37-39]. It has been suggested that patients with refractory heartburn and negative symptom association indices during pH-impedance monitoring performed on therapy should probably be considered as having functional heartburn [40].

Novel impedance-based parameters

Two novel metrics extracted from pH-impedance studies, mean nocturnal baseline impedance (MNBI) and the postreflux swallow-induced peristaltic wave (PSPW) index, have augmented the diagnostic value of pH-impedance monitoring [41,42].

Low baseline mucosal impedance (MI) values, traditionally taken during three separate quiet nighttime periods, have been associated with abnormal mucosal integrity, elevated acid exposure time, and reflux symptoms [43-45]. Further, low MNBI independently predicts response to antireflux therapy [46], especially when the acid exposure time is borderline or inconclusive [47].

The presence of refluxate in the distal esophagus triggers primary peristalsis, allowing delivery of salivary bicarbonate to reverse esophageal mucosal acidification. This can be identified on pH-impedance tracings as a swallow occurring within 30 s of a reflux episode (PSPW), and the proportion of reflux episodes followed by PSPW is termed the PSPW index [48]. Lower PSPW index was reported to segregate GERD patients, especially those with a lack of PPI response, from healthy individuals [48,49].

New techniques

Esophageal mucosal integrity can be measured during esophageal contraction on HRM with impedance and is termed contractile segment impedance (CSI). This method has the added benefits of being convenient and faster [50]. In addition, CSI is expected to have better mucosal contact with the impedance sensor because measurements are obtained during esophageal smooth muscle contraction [50]. A recent study has demonstrated that CSI identifies GERD with equivalent efficacy to MNBI [51].

Esophageal mucosal integrity can also be assessed through a MI device comprised of two radial sensors mounted on a 10 cm balloon that is inflated to insure optimal contact with a long segment of esophageal mucosa. Initial results are promising that MI values correlate with esophageal mucosal inflammation, differentiating erosive and nonerosive GERD from eosinophilic esophagitis and normal patients with better specificity (95% vs. 64%) and positive predictive value (96% vs. 40%) compared with pH monitoring [52-55].

Modern diagnosis of gastroesophageal reflux disease: The Lyon consensus

The recent Lyon consensus delineates parameters on ambulatory reflux monitoring that categorically establish and rule out the presence of GERD [56]. In particular, conclusive evidence for reflux on esophageal testing includes severe erosive esophagitis (LA grades C and D), long-segment Barrett's esophagus, or peptic strictures on endoscopy or distal esophageal acid exposure time >6% on ambulatory pH or multichannel intraluminal impedance-pH monitoring. On the other hand, acid exposure time between 4% and 6% is regarded as inconclusive for GERD. In these patients, adjunctive tests, including HRM and novel impedance-pH metrics (MNBI, PSPW and MI), which may either confirm or reject the diagnosis of GERD. The advantages and disadvantages of diagnostic methods for GERD are summarized in Table 1.

Table 1: Advantages and disadvantages of diagnostic methods for gastroesophageal reflux disease

Methods	Advantages	Disadvantages
GERD questionnaires	Convenience for primary care physicians	Unable to discriminate pathologic reflux from functional heartburn
PPI test	Usefulness in primary care for patients without alarm symptoms	Low specificity: 24%–65%
Endoscopy	Diagnosis of erosive esophagitis, Barrett's esophagus, and eosinophilic esophagitis	Poor sensitivity; 70% of patients have normal mucosa
Wireless pH-metry	Prolonged monitoring to overcome day-to-day variability; better patients' tolerance	Expensive and endoscopy-required
pH-impedance	Detection of acid/nonacid reflux, aerophagia and supragastric belching	Day-to-day variability and unpleasant for patients
MNBI, CSI and PSPW	Augmentation for distinction between patients with GERD versus functional heartburn	Requires manometry and/or catheter-based pH-impedance; time-consuming manual calculations
Mucosal impedance	Direct measurement of mucosal integrity all along esophageal axis and radial distribution to identify NERD, erosive esophagitis, Barrett's esophagus, and eosinophilic esophagitis	Undergoing validation studies and endoscopy-required

GERD: Gastroesophageal reflux disease, PPI: Proton pump inhibitor, MNBI: Mean nocturnal baseline impedance, CSI: Contractile segment impedance, PSPW: Postreflux swallow-induced peristaltic wave, NERD: Nonerosive reflux disease

Managements

After confirmation of GERD, the treatment commonly starts with PPI therapy and complementary lifestyle measures for patients without alarm symptoms. Optimizing PPI therapy and discussing appropriate administration are critical factors in ensuring compliance and increasing dosage to twice daily can be considered in selective patients with persistent symptoms. Patients with continued symptoms can be evaluated with tests of esophageal physiology, to better determine their disease phenotype and optimize treatment. Primary care providers should be cautious to inquire origin of symptom generation to be reflux or nonreflux mechanism when symptoms respond poorly to optimal PPI therapy.

Proton pump inhibitors

Short-term PPI therapy heals esophagitis in 72%–83% of patients (compared with 18%–20% for placebo)[57] but resolves heartburn in only 56%–77% of patients with esophagitis (with 4–12 weeks of therapy) [10]. PPIs maintain healing of erosive esophagitis in 93% of patients (compared with 29% of patients for placebo) [58]. The standard dose of PPIs resolves heartburn in only 37%–61% of patients without erosive esophagitis or with uninvestigated heartburn [59]. Patients with a poor or incomplete treatment response to PPIs are recommended to have esophageal pH monitoring to confirm the evidence of pathological acid reflux as a cause of symptoms [60]. Response rates are lower in patients with atypical symptoms of GERD, indicating potential differences in mechanisms of pathogenesis. Current updates of personalized managements are summarized in the Figure 1.

Potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs) competitively and reversibly act at the potassium-binding site of the proton pump. Compared to PPIs, P-CABs accumulate more in the parietal cells' canaliculi. In addition, P-CABs bind to both the active and inactive forms of the proton pump resulting in a faster and longer duration of the anti-secretory effect than PPIs [61,62]. Overall, P-CABs were noninferior to PPIs in healing erosive esophagitis and maintaining healed erosive esophagitis. P-CABs have demonstrated better and earlier healing of advanced erosive esophagitis (grade C or D) than PPIs [63-66].

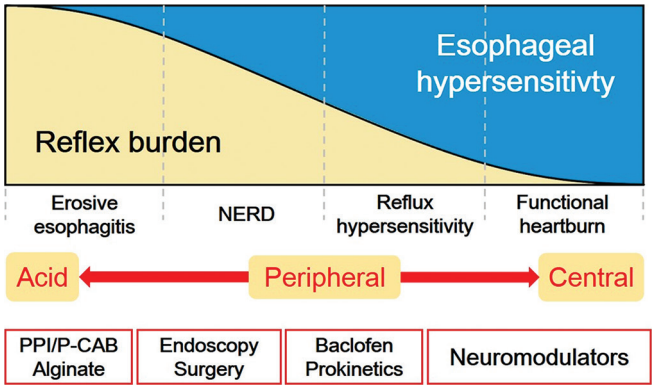

Figure 1: Individualized management of GERD according to precise phenotyping. NERD, non-erosive reflux disease; PPI: Proton pump inhibitor; P-CAB: Potassium-competitive acid blocker, GERD: Gastroesophageal reflux disease, NERD: Nonerosive reflux disease

H2 receptor antagonists

H2-receptor antagonists (H2RAs) competitively inhibit histamine receptors in the gastric parietal cell. H2RAs allow esophagitis healing in 41% of patients as compared with 18%–20% placebo [67]. H2RAs relieve heartburn in 48%–56% after 4–12 weeks of treatment [68]. H2RAs can be used as part of an alternative for patients with uncomplicated GERD following PPI-induced remission of symptoms. This step-down therapy is generally only recommended for patients without erosive esophagitis or BE.

Reflux-reducing agents

Baclofen, a gamma-aminobutyric acid B receptor agonist reduces TLESRs and reflux episodes in healthy volunteers as well as patients with GERD [69]. However, central side effects from baclofen (dizziness and somnolence) may limit its utility, and data regarding long-term symptom benefit are conflicting.

Adjunct medications

Antacids are basic aluminum, calcium, or magnesium compounds and are used to control intermittent esophageal symptoms, especially heartburn. Their advantage is fast onset and fast relief of symptoms. Antacids do not maintain longer symptoms relief, help erosive esophagitis healing,

or prevent GERD complications, like Barret's esophagus or erosive esophagitis [70]. Alginates form a raft and create a physical barrier against reflux in the acid pocket [71]. When alginates are combined with antacids, combination is more efficacious at relieving heartburn and acid reflux than antacids alone [72]. Prokinetic agents (metoclopramide, domperidone, and mosapride) are potentially useful for reducing symptoms of GERD by increasing lower esophageal sphincter basal tone, increasing esophageal acid clearance, and accelerating gastric emptying. However, a meta-analysis of randomized studies found only modest reductions in symptom scores when prokinetics were added to PPI therapy [73].

Nonpharmacological management

Anti-reflux surgery as surgical fundoplication can reduce all types of reflux, including weakly acidic and nonacid. Surgical fundoplication is at least as effective as continued PPI therapy and, in some studies, was even superior to pharmacological therapy in controlling GERD symptoms [74-76]. Criteria of candidates for surgical fundoplication include patients with large hiatal hernia, regurgitation as the predominant symptom, abnormal acid exposure time, poor healing of erosive esophagitis despite maximum PPI dose, and those with symptoms that correlate with gastro-esophageal reflux despite maximum PPI dose [77,78].

Endoscopic anti-reflux procedures are considered as an alternative for anti-reflux surgery and chronic PPI treatment. Initially, endoscopic fundoplication and radiofrequency energy delivery are two endoscopic procedures for the treatment of GERD [79]. Recently, antireflux mucosectomy and antireflux mucosal ablation are novel endoscopic intervention to induce cardiac scar formation that reduces the opening of the EGJ through the healing process [80-82]. Endoscopic therapies for GERD have demonstrated short-term effectiveness such as improved health-related quality of life, reflux symptom severity, acid exposure time, and reduced PPI use, but long-term outcomes remain unclear [83-86]. Of note, criteria of candidates for endoscopic procedures include typical GERD symptoms (heartburn and/or regurgitation), low-grade erosive esophagitis (grade A or B) or NERD, negative of major motility disorders, hiatal hernia <3 cm in size, and complete or partial response to PPI treatment [87].

Conclusions

The pathogenesis of GERD involves impaired EGJ barrier, esophageal hypomotility, refluxate and acid burden, psychiatric comorbidity, and hypervigilance. Acid-inhibition therapy is the mainstay of medical treatment for GERD. Recent advances in diagnostic testing for GERD have shed light on tailored management.

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