Best Practice & Research Clinical Gastroenterology 40-41 (2019) 101649

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Reflux esophagitis, functional and non-functional

Serhat Bor

Professor in Gastroenterology, Ege University, School of Medicine, Division of Gastroenterology, Ege Reflux Group, Izmir, Turkey

ARTICLE INFO

Article history:
Received 6 June 2019
Received in revised form
7 August 2019
Accepted 12 August 2019

Keywords:
Gastroesophageal reflux disease
Esophagus
Epidemiology
Epithelial resistance
Upper gastrointestinal endoscopy
Proton pump inhibitor
24-h intraesophageal pH-impedance

ABSTRACT

The pathogenesis of gastroesophageal reflux disease has been explained by acid-peptic model. However, related with the progress of the diagnostic modalities, another phenotypical group of patients were defined and called "functional disorders of the esophagus". These patients are important because diagnosis is particularly difficult, co-morbid disorders especially psychiatric diseases are common, proton pump inhibitor response is low, and surgical results are very poor. Simpler and translational science studies are required in functional groups in order to differentiate from acid-peptic disorders. New and more accurate diagnostic modalities as well as therapeutic approaches are strongly needed in this particularly new and exciting era, especially in the effect of neuromodulators. Current diagnostic modalities should also be evaluated and in fact, normal values should be established. New medications, especially acting at the level of esophageal epithelium and intercellular spaces, might shift the paradigm.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common chronic disease with a prevalence of about 20% in many countries. However, there is still a lack of definitive diagnostic and therapeutic approaches. Recently, about half of GERD patients were defined under a new category entitled "functional". Upon defining new phenotypes, new diagnostic approaches and therapeutic modalities have been studied. However, initiator factors of the disease are still unknown and there is a lack of gold-standard diagnostic modalities, such as the normal values of 24 intraesophageal pH-impedance. This chapter starts from definition and prevalence and continues to summarize diagnostic and therapeutics, with particular emphasis on the difference between functional vs non-functional phenotypes.

Definition and clinical manifestations

Gastroesophageal reflux disease (GERD) is a chronic disorder that is caused by abnormal reflux of acid, pepsin, bile and pancreatic enzymes. Prolonged exposure of the esophagus to gastric contents leads to typical or atypical symptoms and/or findings [1]. Typical GERD symptoms are heartburn and/or regurgitation, while atypical symptoms include laryngopharyngeal and pulmonary symptoms, such as cough, hoarseness, non-cardiac chest pain and dental erosions [2]. The relationship of some disorders including sinusitis, pharyngitis, pulmonary fibrosis and recurrent otitis media with GERD is still debatable.

It is possible to classify the disease as functional and non-functional GERD. Recent Rome classification defines functional esophageal disorders in five different subgroups including functional chest pain, functional heartburn, reflux hypersensitivity, globus and functional dysphagia [3]. In order to make a diagnosis of functional disease; upper gastrointestinal endoscopy (EGD) of the patient should be normal and there should be no evidence of stricture, eosinophilic esophagitis and motor disorders.

From a physician's point of view, an ideal patient with GERD has typical symptoms, a good response to proton pump inhibitors (PPIs) and/or erosive esophagitis. However recent developments have revealed different disease patterns/phenotypes and these phenotypes require different therapeutic approaches with different success rates. Some phenotypes and related conditions such as reflux hypersensitivity (RH) or functional heartburn (FH) are difficult to manage.

Pathogenesis

GERD is a result of an imbalance between the aggressive forces within the refluxate and defensive mechanisms of the esophagus. Finally, symptoms and/or esophagitis develop when noxious substances in the refluxate have enough time in contact with the

E-mail address: serhat.bor@ege.edu.tr.

https://doi.org/10.1016/j.bpg.2019.101649
1521-6918/

epithelium to overcome tissue resistance. Different pathogenic mechanisms that have been proposed are presented in Table 1.

Antireflux barriers at the gastroesophageal junction

Antireflux barriers such as LES and crural diaphragm are the primary preventive mechanisms against reflux events and they are supported by the phrenoesophageal ligament and the sling muscle fibers of the gastric cardia. The association of hiatus hernia and GERD is controversial. Symptoms of GERD have been shown in only 10% of patients with hiatus hernia. In the patients evaluated with endoscopy because of dyspeptic symptoms, 42% of those with a hiatus hernia did not have esophagitis while 63% of patients with endoscopically confirmed esophagitis had hiatus hernia. Patients without a hiatus hernia or with a small hiatus hernia had similar abnormalities of lower esophageal sphincter function and acid clearance; however, patients with a large hiatus hernia showed shorter and weaker lower esophageal sphincter, greater reflux and less effective acid clearance [4]. It is possible that hiatus hernia might be the result of GERD and a contributing factor for advanced disease but not the initiator of the disease process.

An interesting but old study showed that while the patients with symptomatic GERD without any histopathological findings had normal sphincter pressure, patients with definite inflammatory changes had pressures significantly lower than normal [5]. These data implicate that decrease in LES pressure starts with inflammatory changes and LES is normal in the early stages of the disease. Patients with GERD complications like stricture or Barrett's esophagus have longer duration of symptoms and significantly lower esophageal sphincter pressure [6].

TLESRs have been suggested as one the major causes of gastroesophageal reflux in normal subjects and in patients with GERD, especially if LES pressure is normal [7]. The prevalence of reflux during transient lower esophageal relaxations varies in a wide range; between 9% and -93% [8], and TLESR occurs at 2–6 episodes/h in normal volunteers, compared to 3–8 episodes/h in GERD patients [9], but in some studies the exact frequency may be overestimated because of the pharyngeal irritation of the catheter. TLESRs have been shown to be the primary factor in endoscopy-negative, symptomatic GERD patients; however, since the TLESRs decrease with the severity of the disease, the importance of this concept becomes less prominent in patients with advanced disease.

Table 1
Possible pathogenetic factors of GERD.

1. Antireflux barriers at the gastroesophageal junction
   (a) Hiatal hernia
   (b) Lower esophageal sphincter (LES), crural diaphragm
   (c) Transient lower esophageal sphincter relaxations (TLESRs)
   (d) Swallow-induced LES relaxations
2. Impaired esophageal clearance
   (a) Low amplitude or simultaneous esophageal contractions
   (b) Saliva
3. Gastric factors
   (a) Gastric acid hypersecretion
   (b) Delayed gastric emptying
   (c) Gastric distension
   (d) Abnormal antropyloroduodenal antireflux; bile, pancreatic enzymes
4. Impaired esophageal mucosal defense mechanisms
5. External factors
   (a) High-fat foods
   (b) Hypertonicity or warm drinks (heat stress)
   (c) Smoking
   (d) Ethanol
   (e) Medications
6. Increased esophageal sensitivity
7. Esophageal microflora

Impaired esophageal clearance

During an episode of reflux, luminal acid clearance mechanisms play an important role to limit the duration of contact between the esophageal epithelium and refluxate. The factors contributing to luminal clearance include gravity, peristalsis and specifically for acid clearance, bicarbonate secretion from the salivary and esophageal glands [10]. Both primary and secondary peristalsis are important in esophageal emptying in GERD and assessment of peristaltic function during swallowing is valuable for the severity of the disease [11]. It has been reported that weak peristalsis with a pathologic number of large breaks measured with high resolution manometry was associated with high acid exposure and delayed reflux clearance in the supine position in GERD patients [12].

Saliva is an underestimated issue and only a limited number of studies have been performed. Saliva contains bicarbonate, which buffers acid, reduces acid exposure time and rich in growth factors, such as epidermal growth factor, which promotes mucosal repair. When compared with the exposure of the lower esophageal mucosa to acid and pepsin, the exposure of the upper esophageal mucosa results in the secretion of a significantly higher amount of salivary bicarbonate, up to 3-fold [13]. In a study with 10 non-erosive reflux disease (NERD) patients, it has been shown that salivary volume, bicarbonate glycoconjugate (mucin), protein, TGF-alpha and EGF output were significantly higher during intra-esophageal mechanical and chemical stimulation than that of controls [14]. However, these results should be confirmed by other groups and clinical significance should be established.

Gastric factors

These factors include acid, pepsin, bile and pancreatic secretions. A large prospective study about gastric secretory factors of GERD showed that the rate of acid secretion in GERD patients is similar to that of healthy volunteers [15]. In a recent study, we evaluated the levels of gastric pepsin in different phenotypes of GERD and functional heartburn. No difference was shown [16]. Bile acids can decrease the barrier function of esophageal epithelium. Vaezi et al. showed that majority of the duodenogastroesophageal reflux (DGER) episodes (70–91%) occurred in an acidic environment and more severe forms of GERD had higher (89–100%) exposure to the simultaneous damaging effect of acid and bile salts [17]. There was no esophagitis in the group with only DGER, suggesting that DGER may not be damaging by itself in the absence of acid reflux.

There are conflicting results about the importance of delayed gastric emptying and these discrepancies seem to be related to the technique used for measuring gastric emptying (ultrasound or scintigraphic study).

Impaired esophageal mucosal defense mechanisms

Esophageal epithelial resistance is the combination of different dynamic protective factors (Table 2). These factors work in harmony and protect the epithelium against different endogenous and exogenous noxious agents (cigarette smoke, ethanol, hypertonicity, heat or medications such as non-steroidal anti-inflammatory drugs) [18–22]. These noxious agents increase the susceptibility to acid, and also might convert an innocuous concentration of acid into a damaging agent [23]. Esophageal defense mechanisms can be classified into three categories; pre-epithelial, epithelial and post-epithelial. Compared to that in the stomach and duodenum, the pre-epithelial defense in esophagus is weak because of the absence or inadequate mucous layer or bicarbonate secretion into the lumen. Epithelial defense mechanisms consist of both structural

Table 2
Factors contributing to tissue resistance of esophageal epithelium (adapted from 10).

1. Preepithelial defenses
   a. Mucus
   b. Unstirred water layer
   c. Secreted/transmitted bicarbonate ions
2. Epithelial defenses
   a. Apical cell membranes
   b. Apical junctional complex
      i. Tight junctions
      ii. Adherens junctions
      iii. Intercellular glycoconjugate
   c. Cytosolic pH regulation (acid extruders)
      i. Sodium-hydrogen exchanger
      ii. Sodium-dependent chloride-bicarbonate exchanger
   d. Cytosolic buffers
      i. Protein
      ii. Phosphates
      iii. Bicarbonate (carbonic anhydrase-generated)
   e. Extracellular buffers
      i. Bicarbonate
      ii. Phosphates
      iii. Protein
      iv. Cell reparative defense; restitution and replication
3. Postepithelial defense
   a. Blood supply
   b. Tissue acid-base balance

and functional components [24] (Fig. 1). Prolonged exposure of esophageal epithelium to luminal acid, pepsin and other noxious agents result in an alteration on the apical junctional complex, increase in intercellular permeability and, structurally, in dilated intercellular spaces (DIS). DIS lead to decreased transepithelial resistance, and increased esophageal mucosal permeability. Acid reflux, bile acids and pancreatic enzymes and/or psychological stress can modulate the development or persistence of DIS. These findings implicate that GERD, at least in part, is the result of an impairment in tissue resistance. Once the disease is initiated, other factors such as low LES pressure, frequent TLESRs, failed peristaltic contractions, and the presence of a hiatus hernia play an important role to perpetuate the disease. Moreover, these defects not only may perpetuate the disease but contribute to its progression [25].

Another weakness of the esophageal epithelium is the repair mechanisms following the acid-peptic damage. Esophagus has a multicellular layer of tissue and repair mechanisms are much slower (days to weeks) than that in the stomach, through cell replication and migration with manifestation of basal cell hyperplasia.

The postepithelial defense in the esophagus is principally provided by blood supply. Blood flow delivers oxygen, nutrients, and bicarbonate and removes H^+ and CO_2. As an adaptive mechanism, luminal acidity in esophageal blood flow increases.

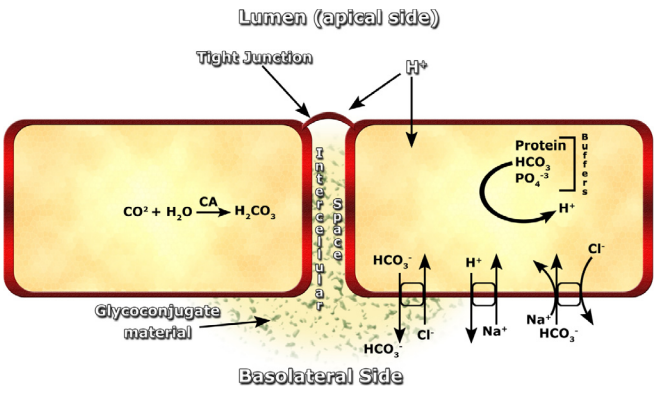

Fig. 1. The defense mechanisms in the esophageal epithelium [26].

Increased esophageal sensitivity

The role of esophageal sensitivity has been presented recently in the pathogenesis and changed the paradigm of GERD. The mechanisms underlying the symptoms of GERD are not only related to pathological acid exposure but also associated with enhanced peripheral and central sensitivity of the esophagus, especially in some phenotypes of GERD. Both mechanisms −pathological acid exposure and/or hypersensitivity- play important roles however their relative roles change throughout the spectrum of phenotypes. While pathological acid exposure is the predominant factor in erosive esophagitis, hypersensitivity is the main mechanism in patients with normal upper gastrointestinal endoscopy and acid exposure. This approach has strong clinical relevance which might help to understand PPI-unresponsive cases and the therapeutic role of neuromodulators.

Increased esophageal sensitivity has been studied in some patients with different methodologies such as Bernstein test, esophageal balloon distension using a barostat balloon (mechanosensitivity), multimodal esophageal stimulation (thermal, electrical, mechanical, and chemical stimulation) [27]. However, the number of subjects was small in many studies and some studies were performed in healthy volunteers only. Interestingly, in a small study with 11 patients and 10 controls, patients showed increased perception of acid perfusion but not of esophageal distension, which implicates that chemosensitivity but not mechanosensitivity is correlated with heartburn [28]. Rao et al. studied the sensory perception and biomechanical properties of esophagus at three different levels and LES in 11 healthy volunteers using impedance planimetry [29]. They found that proximal esophagus was more sensitive and sensitivity decreased towards the distal esophagus, however the striated muscle portion was less compliant than the smooth muscle portion.

Cicala et al. analyzed the spatio-temporal characteristics of reflux events and perception of typical symptoms in 45 patients with NERD (both pH-negative and positive) and 20 patients with erosive esophagitis [30]. pH-negative NERD patients showed the highest percentage of proximal reflux when compared to the patients with erosive esophagitis and they were also highly sensitive to proximal reflux episodes. They concluded that the presence of acid within proximal esophagus represents the main determinant of the presence of typical symptoms of NERD and a normal 24-h pH monitoring. Different but still limited studies showed that NERD patients are hypersensitive to thermal, mechanical, and chemical stimulation compared to healthy volunteers [27].

Peripheral mechanisms of esophageal hypersensitivity

Although impaired defense mechanisms and esophageal hypersensitivity are different concepts, decreased transepithelial resistance of the esophageal epithelium is an important peripheral mechanism of esophageal hypersensitivity to reflux. DIS allow the noxious agents to diffuse into the epithelium, reach to the nerve endings, which are located in the submucosal layer, and increase symptom perception. Epithelial cell injury and death possibly trigger both inflammatory and proliferative responses. An alternative explanation for epithelial disruption in GERD was raised by Souza et al. [31]. In their rat model, they observed that the first sign of inflammation in the epithelium is infiltration of the submucosa by lymphocytes, followed by neutrophils to involve the epithelial surface. This inflammatory response precedes the proliferative response with the evidence of basal cell and papillary hyperplasia. These changes eventually result in surface erosions.

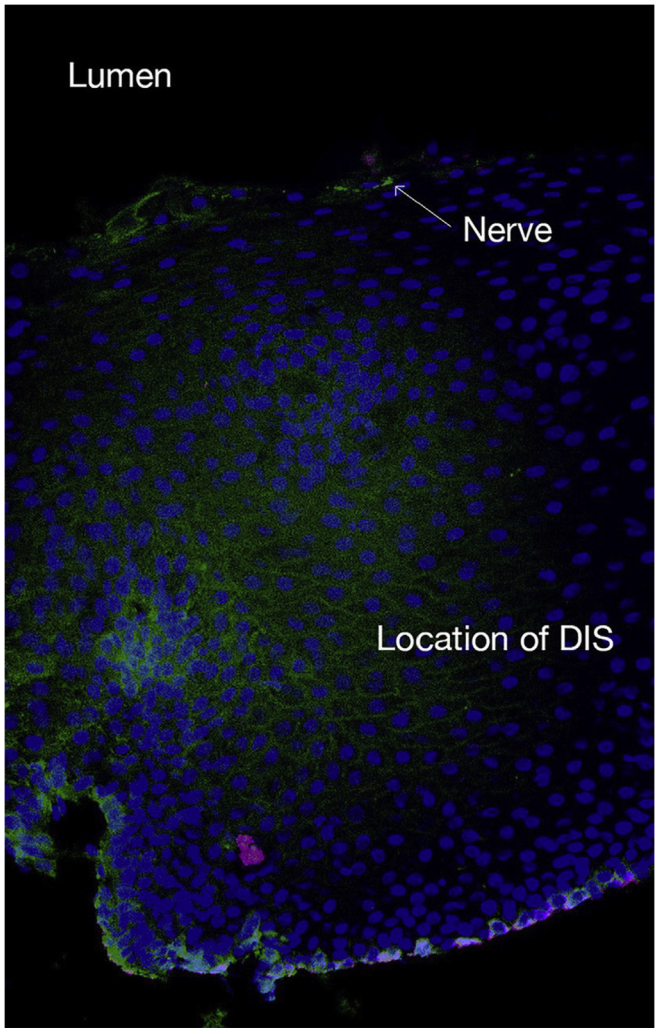

Fig. 2. Nerve endings in NERD are located close to the lumen [32].

Woodland et al. obtained esophageal biopsies from patients with different GERD phenotypes and examined the presence and location of nerve fibers. Fibers in NERD were close to the esophageal lumen with DIS in the basal layer (Fig. 2). In all groups and healthy volunteers, nerve localization within the distal esophageal mucosa was deeper than that in the patients with NERD. These findings might explain the role of hypersensitivity in NERD patients [32].

Central mechanisms of esophageal hypersensitivity

Central sensitization is assumed to play an essential role in esophageal hypersensitivity. However, majority of the studies have been performed in patients with non-cardiac chest pain, not in patients with heartburn or regurgitation. Esophageal acid stimulation sensitizes the cingulate and insula cortex to subliminal and liminal non-painful mechanical stimulations [33]. This situation leads to the amplification of incoming signals and lack of inhibition by descending anti-nociceptive pathways [27].

The effects of negative and neutral emotional states on the perception of non-painful esophageal distension were evaluated in 8 healthy subjects with functional magnetic resonance imaging (fMRI). If a negative emotional feeling was applied, the same stimulus was perceived more intensely. This was associated with more increased cortical activity in the anterior insula and the dorsal anterior cingulate gyri than that during a neutral emotional context [34,35].

These are regulated by factors that affect central mechanisms, such as stress, anxiety, and personality traits [36]. Recently we and some other researchers showed that stressful life events, high levels of depression, anxiety and somatisation, and neurotic personality traits might all be related to the clinical features of GERD. In a study evaluating different GERD phenotypes and functional heartburn, we showed that the prevalence of major depressive disorder in functional heartburn (FH) is significantly higher than that in NERD, and depressive disorders was significantly higher than that in both NERD and erosive esophagitis patients (Table 3) [37]. We conclude that patients with non -erosive GERD have more psychiatric comorbidity than erosive groups and this might be a bi-directional effect. While psychiatric comorbidity increases symptom perception, more severe and PPI refractory symptoms might increase the prevalence of psychiatric problems.

Epidemiology

It is difficult to estimate the true prevalence of GERD because of the lack of gold standard diagnostic modalities. As invasive procedures are needed, it is even more difficult to detect functional phenotypes. High-quality prevalence studies have been performed in the last 20–25 years in Western countries and more recently in Eastern countries. Prevalence studies have been using different questionnaires as well as different diagnostic criteria. This situation makes it very difficult to compare the epidemiologic results from different geographic areas or groups derived from different studies. Besides, GERD is possibly one of the most common chronic diseases in adults in developed countries. If all studies from Western countries were to be evaluated cumulatively, the prevalence of heartburn and acid regurgitation would be 23% and 16%, respectively [38]. Studies from South-East and East Asian populations reveal a much lower prevalence of 2.5–8.2% than Western studies. An interesting finding from those studies indicates that Eastern countries show a different symptom profile, namely a lower incidence of heartburn, and a higher incidence of regurgitation [39].

About 65–70% of patients with GERD have normal endoscopy, and these patients are considered to have NERD; however, they are further classified into different phenotypes according to acid exposure and symptom-reflux association. It is very difficult to estimate the true prevalence of phenotypes and functional heartburn except Barrett's esophagus and erosive esophagitis. A study by

Table 3
Prevalence of psychiatric disorders in GERD subgroups [37].

Psychiatric Disordes	Erosive esophagitis [39]	NERD [44]	Functional heartburn [20]	Esophageal hypersensitivity [11]	General population
Major depression	23.1	18.2	45	27	5.6
Dysthymic disorder	12.8	11.4	20	18.2	1.6
Generalized Anxiety Disorder	20.5	4.5	0	45	0.7
Panic Disorder	5.1	4.5	5	0	0.4
Social Anxiety Disorder	25.6	18.2	15	18.2	1.8
Somatisation Disorder	10.3	2.3	0	18	8.6

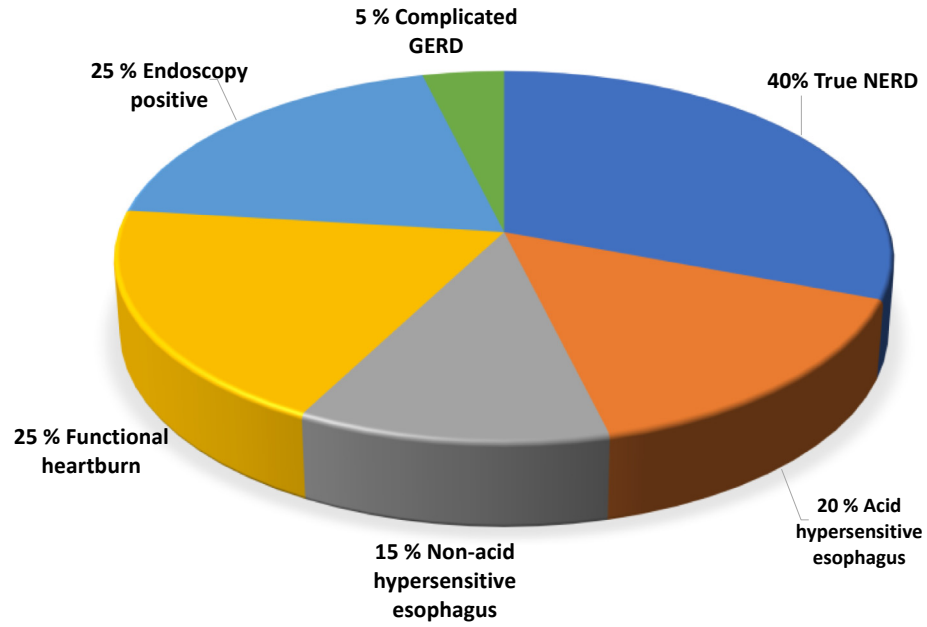

Fig. 3. Distribution of NERD patients according to Endoscopic and 24h intraesophageal impedance-pH testing (adapted from 40).

Zentilin et al. showed that 25% of patients with typical reflux symptoms are classified as erosive esophagitis, and 5% have complicated GERD, including Barrett's esophagus. Among patients with normal endoscopy; 40% have true NERD; 20% have esophageal hypersensitivity to acid; 15% have esophageal hypersensitivity to non-acid reflux and 25% have functional heartburn (Fig. 3) [40]. However, these figures are probably different in non-western countries with a lower prevalence of Barrett's esophagus and erosive esophagitis [38].

Diagnosis

It is possible to say that following the marketing of PPIs there is no major advance in medical treatment, but diagnostic technologies are rapidly advancing, and new technologies are being launched while some others are being abandoned (Table 4) [41]. These new technologies certainly give more accurate data and better detection of different esophageal diseases. They might assist in the development of new medications or improve the therapeutic outcomes of the current ones.

Different phenotypes have been defined according to upper gastrointestinal endoscopy findings and 24 h intraesophageal impedance-pH monitoring. It is not difficult to make a diagnosis of erosive esophagitis or Barrett's esophagus however, functional part of the diagnosis is more difficult especially in reflux hypersensitivity and functional heartburn.

Patients with reflux hypersensitivity suffer from typical symptoms with a correlation between symptoms and reflux episodes (symptom association probability and symptom index) on 24-h intraesophageal pH (or pH-impedance) monitoring, but acid exposure time and upper gastrointestinal endoscopy should be normal. Eosinophilic esophagitis and major esophageal motor disorders should be excluded [3].

Functional heartburn is a difficult diagnosis. According to Rome IV criteria and for many authors, it is not a part of GERD spectrum. These patients define typical GERD symptoms but have no response to PPI therapy, esophageal acid exposure is normal and no association can be shown between symptoms and reflux episodes. Other possible reasons should be excluded such as eosinophilic esophagitis and major esophageal motor disorders as well.

The presence of typical symptoms (heartburn and regurgitation) and a good response to PPIs are practical diagnostic tests. However, in real life different diagnostic tests might be needed in some cases. Indications for further diagnostic tests are treatment failure (PPI unresponsiveness, diagnostic uncertainty) and complications, especially in the presence of atypical (extraesophageal) findings of GERD [42].

Proton pump inhibitor trial

Many physicians worldwide lack sophisticated diagnostic modalities; therefore, they mainly diagnose the patients based on symptoms and upper gastrointestinal endoscopy findings. The PPI response to typical symptoms, which is called the “PPI test”, is a primary diagnostic tool [43]. It is non-invasive, easily applicable, and cost-effective. The specificity of the test for heartburn and acid

Table 4
Diagnostic tests in GERD.

Tradional tests	New tests	Abondoned tests
White-light upper Gi endoscopy	24 h intraesophageal pH/impedance monitoring	24 h intraesophageal Bilirubin monitorization (Bilitec)
24 h intraesophageal pH monitoring	High resolution manometry	Barium swallow radiology
Conventional manometry	Novel endoscopic technologies	Laryngeal pH monitoring
Wireless pH monitoring	Impedance planimetry	Radionuclide scintigraphy
	Mucosal impedance measurements	Bernstein test
	Pepsin detection from saliva	

regurgitation were found to be high in early studies, as 89% and 95%, respectively [44]. Different than these early promising studies, others reported low response rate and this might decrease the value of the therapeutic trial approach [45]. However, the studies reporting low response rate might also be criticized. Sixteen PPI trial studies have been assessed by a GERD consensus group [46]. There was no agreement between the studies for the dose, time of the trial or definition of "response"; 50%–75% recovery was generally accepted as threshold. Most of these studies used a high dose (double) of PPI, and the median time was 14 days (Table 5). The cumulative sensitivity of the PPI trial was 82.3%, the specificity was 51.5%, the positive predictive value was 79%, and the negative predictive value was 56.9%, which implicates that a negative test does not exclude the disease. This approach is still the first step of the diagnosis.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy is the most commonly used diagnostic technique following the PPI test, and allows direct visualization of the esophageal mucosa and demonstrates erosive esophagitis, stricture and Barrett's esophagus. It also allows taking biopsies, especially for the diagnosis of eosinophilic esophagitis, and prove Barrett's esophagus. Erosive esophagitis is found in only 30% of the patients and in less than 10%, if the patient is already on PPIs [47]. Los Angeles (LA) Grade C, D and possibly B esophagitis are sufficient for the diagnosis [48]. However, LA Grade A esophagitis can be observed in 8.5% of asymptomatic controls [49]. Esophageal histology has limited value except for Barrett's esophagus and eosinophilic esophagitis. Many different histopathological criteria have been proposed for the differential diagnosis of NERD, reflux hypersensitivity and functional heartburn. A structured histopathological evaluation suggested that papillary elongation, basal cell hyperplasia, dilated intercellular spaces, intraepithelial inflammatory cells, necrosis and erosions might be useful. However, histopathological findings can overlap between the groups, and are not conclusive for the differential diagnosis of functional and non-functional phenotypes of GERD [48]. Some immunohistochemical markers such as proteinase-activated receptor-2, interleukin-33, G-protein coupled receptor 84, and triggering receptor expressed on myeloid cells (TREM)-1 signaling pathway [50] have been studied; however none of them show a significant discrimination value. The detection of E-cadherin in the serum, which is a junctional protein, was suggested as a diagnostic biomarker [51]; however, we could not confirm this finding [52].

Several imaging modalities including magnification endoscopy, electronic chromoendoscopy (such as narrow band imaging and I-scan), and confocal laser endomicroscopy have been investigated [53]. Whether new endoscopic techniques add a new dimension to diagnosis than conventional high-definition white-light endoscopy is still debatable [54]. Electronic chromoendoscopy and confocal laser endomicroscopy are possibly the most promising devices so far; however, because of the lack of a gold standard technology for diagnosing NERD and phenotypes, it is difficult to objectively measure the diagnostic value of new technologies.

Wireless capsule endoscopy

Wireless capsule endoscopy (WCE) is a feasible, safe and well-accepted technique for the rest of the gastrointestinal tract; however, it has limited value for esophagus because of the rapid esophageal transit and the localization of common pathologies such as Barrett's esophagus, esophageal malignancies and varices near the esophagogastric junction [55]. Because of these limitations, WCE cannot replace upper gastrointestinal endoscopy except the patients who refuse the procedure or where contraindicated. New technical progresses including remote magnetic control systems, flexible spectral imaging color enhancement system, adding a self-folding microgripper might increase in value of WCE.

24-h intraesophageal ambulatory pH or pH-impedance monitoring

24-h intraesophageal (only) pH monitoring without impedance documents excessive acid reflux in patients with symptoms of GERD but without endoscopic esophagitis, assesses reflux frequency and symptom association. Although it is an important technique, it is not the gold standard diagnostic method for GERD. Nevertheless, 24-h conventional intraesophageal pH testing failed to diagnose abnormal acid exposure in up to 40% of patients with erosive esophagitis and more in those with NERD when the percentage total time for pH < 4 was used as the only criterion.

Among the pH monitoring metrics, acid exposure time (AET) is the most reproducible one [56]. According to the Lyon consensus AET <4% is excepted normal (physiological), >6% is *considered* as abnormal and the intermediate values are inconclusive. The probability of a relationship of a reflux event with an episode of

Table 5
PPI trials [46].

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Active ingredient	Usage	Duration	The number of patients
Xia et al. [10]	91.7	47.1	37.9	94.1	Lansoprazol	30 mg AM	28 days	36
Pace et al. [23]	95.4	36.4	85.5	66.7	Omeprazol	20 mg AM and 20 mg PM	15 days	544
Pandak et al. [9]	68.8	27.3	40.7	54.5	Omeprazol	20 mg AM ard 20 mg PM	14 days	38
Bate et al. [7]	68.8	57.7	66.7	60.0	Omeprazol	40 mg AM	14 days	58
Fass et al. [31]	100.0	42.9	72.4	100.0	Omeprazol	40 mg AM and 20 mg PM	14 days	35
Schenk et al. [2]	68.2	63.2	68.2	63.2	Omeprazol	40 mg AM	14 days	41
Cho et al. [28]	76.6	55.6	92.5	25.0	Lansoprazol	30 mg AM and 30 mg PM	14 days	73
Dent et al. [27]	53.8	64.6	75.2	41.3	Esomeprazol	40 mg AM	14 days	296
Kim et al. [25]	81.3	73.1	65.0	86.4	Rabepfazol	20 mg AM and 20 mg PM	14 days	42
Dekel et al. [30]	88.9	60.0	80.0	75.0	Rabepfazol	20 mg AM and 20 mg PM	14 days	14
Aanen et al. [29]	89.1	19.0	70.7	44.4	Esomeprazol	40 mg AM	13 days	67
Fass et al. [3]	78.3	85.7	90.0	70.6	Omeprazol	40 mg AM and 20 mg PM	7 days	37
Fass et al. [6]	80.0	57.1	90.3	36.4	Omeprazol	40 mg AM and 20 mg PM	7 days	42
Bautista et al. [11]	77.8	81.8	77.8	81.8	Lansoprazol	60 mg AM and 30 mg PM	7 days	40
Juu1-Hansen et al. [21]	100.0	5.6	66.7	100.0	Lansoprazol	60 mg AM	7 days	52
Juu1-Hansen et al. [8]	85.3	50.0	72.5	68.8	Lansoprazol	60 mg AM	5 days	56
Cumulative	82.3	51.5	79.0	56.9	7 Omeprazol 5 Lansoprazol 2 Esomeprazol 2 Rabepfazol	High doses in all: bid Median test for 14 days		

Fig. 4. Relationship between symptoms and reflux episodes in a patient with reflux hypersensitivity (Ege University, School of Medicine, Motility Laboratory).

heartburn or regurgitation is used to assess reflux-symptom association [57] (Fig. 4). This concept has been used to diagnose reflux hypersensitivity, which is a GERD phenotype, and functional heartburn, which is possibly a functional disorder out of GERD spectrum.

Currently two metrics are used: symptom index (SI) and symptom association probability (SAP). These tests should be used together, and are predictive of the effect of medical and surgical therapies. If SAP and SI are both positive, then the diagnosis is reflux hypersensitivity; if both are negative, then the diagnosis is functional heartburn (Table 6). It is possible to think that software generated metric values would be sufficient to identify the phenotypes and differentiate functional cases from non-functional. It should be remembered that these definitions are meaningful only if the patient can adjust the equipment; continue regular daily life without dietary or activity limitations and a good sleep pattern, press the symptom button or record on the diary on time. Even if all the above mentioned conditions are met, it is still all about the number of symptoms during the procedure. It is not uncommon that symptoms decrease during the procedure. Both metrics are less reliable in patients with low numbers of reflux events.

Another problem is the day by day variability. Wireless pH capsule results were retrospectively evaluated in 50 PPI-refractory functional heartburn patients. pH monitoring metrics were different in the preceding days than that in day one in 15 out of 50 patients, showed pathologic acid exposure time after the first day of monitoring, which changed their diagnosis from functional heartburn to non-erosive reflux disease [58]. Regardless of some weaknesses of the study (they used only AET and SI, but not SAP, and PPI refractoriness was not clearly defined), this study shows the unsettled nature of GERD phenotypes.

Because of the limitations of classical pH monitoring, 24-h impedance-pH monitoring (MII-pH), a new technology, is now in use and allows the detection of acidic, weakly acidic, and non-acid reflux, as well as liquid and gaseous refluxate [48]. In addition to SAP and SI, new metrics have been proposed with this technology. Baseline impedance, bolus exposure and post-reflux swallow-induced peristaltic wave (PSPW) might increase the value of 24-h MII-pH and help to discriminate phenotypes of GERD from functional heartburn, but data are currently limited [59]. Low baseline or mucosal impedance is a good reflection of inadequate mucosal integrity and dilated intercellular spaces, both reflecting an increase in permeability [60]. Baseline impedance measurement was standardized by Frazzoni et al., by calculating mean nocturnal baseline impedance (MNBI) at three 10-min time periods between 1 a.m. and 3 a.m., away from daytime esophageal physiologic activity. MNBI is lower in functional heartburn compared to GERD phenotypes including reflux hypersensitivity [61].

Another metric, post-reflux swallow-induced peristaltic wave represents the efficacy of esophageal chemical clearance; a peristaltic response to reflux by neutralizing acidified esophageal mucosa with saliva. Impaired esophageal clearance, as evident by lower PSPW index, is observed in erosive disease rather than in NERD [62], functional heartburn and controls (sensitivity 99%–100%, specificity 92%) [61]. A Korean study confirmed that while PSPW might be related with the perception of heartburn, baseline impedance can be associated with dysphagia. This promising results need confirmation from other centers.

Problems in the diagnosis of functional GERD phenotypes

The diagnosis of reflux hypersensitivity and functional heartburn is currently based on the SAP and SI following a normal upper gastrointestinal endoscopy and normal 24 h intraesophageal acid exposure. However as discussed above many problems exist;

Diagnostic problems in the diagnosis of functional GERD phenotypes:

1. There are major differences between the catheters and equipment used and this brings a strong need for normal (super-) healthy volunteer studies (volunteers without typical/atypical GERD symptoms, as well as normal upper gastrointestinal endoscopy and normal high resolution esophageal manometry)
2. Both metrics are defined based on the assumption that the patient can adjust the equipment; maintain regular daily life without dietary or activity limitations and a good sleep pattern, press the symptom button or record on the diary on time. However, this is not the case in some cases.
3. Day-to-day variability in reflux patterns are high and results differ between catheter based- and wireless monitoring equipment- based studies.
4. Some patients cannot clearly identify their symptoms and might use the symptom button for some non-GERD symptoms, such as belching and bloating
5. Metrics are less reliable in patients with low numbers of symptoms
6. New metrics are promising, but need more validation studies
7. The role and the definition of PPI response are not clear and many studies have been performed in PPI-resistant cases.

Management

The major aim of current GERD therapy is symptom relief and improving the quality of life in all patients and mucosal healing in erosive esophagitis group. The possibility of curing symptoms is low.

Table 6
Diagnostic criteria for different GERD phenotypes and functional heartburn.

	Upper GI endoscopy	Acid exposure	SAP (>95%)	SI (>50%)
Erosive reflux disease	Erozive (LA A-D)	–	–	–
Nonerosive reflux disease	Normal	Pathologic	–	–
Esophageal hypersensitivity	Normal	Normal	(+)	(+)
Functional heartburn	Normal	Normal	(−)	(−)

Lifestyle modifications

Despite their common use, lifestyle modifications have limited effects, but should be advised according to the patient's history [63,64]. If a patient states that some foods or drinks trigger the symptoms, dietary modification can be arranged accordingly.

1. Obesity is one of the most important factors, and losing weight is crucial [65]. GERD symptoms (odds ratio 1.43, 95% CI 1.16–1.77) and esophagitis (1.76, 95% CI 1.16–2.68) increases with a BMI> 25 [66].
2. Chocolate, fatty food, sodas should be avoided. Salt and white-wheat bread might be related to symptoms. Low volume, protein-rich and high-fiber food should be preferred. Controlled data, however, are greatly lacking and inconclusive [67].
3. Heavy exercise might increase the symptoms.
4. Smoking is a risk factor in basic science and epidemiologic studies. Alcohol consumption has a direct noxious effect on the esophageal epithelium in basic science studies [18,19]; however, the risk is unclear in epidemiologic studies. The cessation of both is advisable [68].
5. Left lateral position and head elevation are important to protect against night-time reflux, but difficult to adapt and disruptive to the quality of sleep [69]. Their long-term effects are not clear.
6. Interestingly and contrary to dogma, the speed of eating does not impact reflux episodes in normal weight [70] and obese populations [71].

Medical therapy

GERD medications can be classified as follows:

(I) Acid neutralization or inhibition:
   1. Antacids are primarily used only for mild symptoms. The onset of action is rapid, however short-lived. Despite the widespread use of antacids, even placebo-controlled studies have provided conflicting results. Their therapeutic benefit in the treatment of GERD is limited by the lack of well-designed, large, placebo-controlled trials. Thus, it is unlikely that these drugs have a major effect on the disease [72].
   2. H_2 receptor antagonists are still widely used worldwide, particularly for night-time reflux, because of their inhibitory effect on basal acid stimulation [64]. All H_2 receptor antagonists have similar efficacy in symptom relief and in the healing of esophagitis. This drug group has a good safety record, with few side effects. However, some limitations exist, such as a relatively short duration of action, incomplete inhibition of meal-induced acid secretion, and the development of tolerance (as common as 50% of the cases within two weeks, possibly related to the down-regulation of H_2-receptors) [73]. Number need to treat was 7.5% in heartburn without esophagitis and 4.5% for erosive esophagitis cases [74].
   3. Proton pump inhibitors have superior efficacy compared to H_2 receptor antagonists and currently they are the most effective therapeutic option [75]. In terms of heartburn relief, patients with esophagitis have a higher success rate compared to non-erosive reflux patients. The effect of different PPIs was evaluated in a meta-analysis and minor differences were found for both symptom resolution and healing of esophagitis [76].

      Patients with severe esophagitis or Barrett's esophagus need to continue long-term PPI; however, patients with LA A-B esophagitis and NERD groups might be managed with on-demand therapy either with optimal or lowest effective dose of PPIs or other medications such as alginate or H_2 blockers. A recent metaanalysis showed that on-demand therapy shows higher success rate compared to continue PPI therapy.

      PPI response of patients with typical symptoms was reported as 60–65% for heartburn and less than 50% for regurgitation in a review article [77,78]. These cumulative figures are low and possibly related with the inclusion of suboptimal studies. Our personal experience showed much higher response rates in patients who were evaluated with advanced diagnostic tools. Shift from one brand to another might show a minimal effect.

      Response rates of typical GERD symptoms and esophagitis to PPIs in randomized controlled trials are given in Table 7.

(II) **Barrier forming agents**, such as alginate-based formulations [79] demonstrate a faster onset of effect than PPIs and H_2 receptor antagonists and the effect starts within 1 h. Alginate and antacid combination products are more effective compared to antacids for improving heartburn, regurgitation, vomiting, belching and yield a better postprandial esophageal acid exposure [80,81]. It has been shown that regular alginate solution is non-inferior to omeprazole for heartburn-free periods in moderate episodic heartburn [82].

(III) **Prokinetic agents;** Prokinetic agents have not shown to have any consistent effect on reflux symptoms. Both metoclopramide and domperidone have their most documented effects on nausea, and metoclopramide is the only drug broadly available for gastroparesis. The adverse-event profile of these agents must be weighed against clinical benefits and most classical agents, such as bethanechol, metoclopramide, domperidone, and cisapride, either out of market or under supervision (cardiac side effects, particularly fatal arrhythmia) [83]. However, against present day experience from real world data this notice seems to be over-emphasized [84]. Safety studies, particularly those with domperidone, are questionable and clearly metoclopramide is much riskier [85]. A recent meta-analysis showed that domperidone is safe while metoclopramide is not [86] if

Table 7
Response to PPIs for typical symptoms and erosive esophagitis (adapted from 74).

	PPI response %	Placebo response %	Risk ratio for response (95% CI)	NNT
Uninvestigated heartburn	70.3	25.1	2.80 (2.25-3.50)	2.2
Heartburn without esophagitis	39.7	12.6	3.15 (2.71-3.67)	3.7
Heartburn with esophagitis	55.5	7.5	6.93 (3.55-13.52)	2.1
Erosive esophagitis	85.6	28.3	2.96 (2.14-4.11)	1.8
Regurgitation	64.0	46.1	1.40 (1.29-1.47)	5.7
NCCP, (+) GERD testing	74.5	17.2	4.33 (3.04-6.18)	1.7
NCCP, (−) GERD testing	23.6	28.2	0.84 (0.54-1.31)	22.0

NNT: Number of need to treat, NCCP: Non-cardiac chest pain.

following factors are taken into consideration; patients older than 65 years of age; long QT syndromes or medications that prolong the QT interval, with arrhythmia and doses greater than 30 mg/day.

(IV) **Mucosal protective agents.** GERD studies with sucralfate are limited, with small numbers of participants, primarily compared to placebo [87]. Because of the high confidence interval, the effect is not superior to placebo. Currently, its use is limited to GERD in pregnancy, pill esophagitis, caustic ingestion.

(V) **Neuromodulators.** Tricyclic antidepressants and selective serotonin reuptake inhibitors might be used in some phenotypes, such as reflux hypersensitivity and functional heartburn [64]. This is a new and exciting, but underestimated area of research. The majority of the studies have been performed in healthy volunteers and patients with non-cardiac chest pain. A randomized, double-blind, placebo-controlled study in patients with reflux hypersensitivity detected by 24 h pH-impedance monitoring using citalopram 20 mg/day for 6 months showed a significant beneficial effect [88]. In a placebo-controlled study performed in patients with heartburn and normal endoscopy, but failed once daily PPIs, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), was compared with omeprazole in terms of heartburn-free days. In normal 24 h pH monitoring patients (reflux hypersensitivity and functional heartburn), fluoxetine improved heartburn-free days by 57.1% compared with omeprazole and placebo 13.9% and 7.14%, respectively [89]. Different than the previous studies, Limsrivilai et al. evaluated 83 patients with reflux hypersensitivity and functional heartburn and who are refractory to once-daily PPI in a randomized placebo-controlled trial. The patients were divided into two groups to receive 8 weeks of either once-daily imipramine 25 mg or placebo. Imipramine was not superior to placebo to relieve reflux symptoms in patients with esophageal hypersensitivity or functional heartburn [90].

Although, conflicting results have been achieved, neromodulators have been commonly used in functional GERD symptoms.

Anti-reflux surgery

Laparoscopic anti-reflux surgery is an effective long-term therapeutic option in well-selected patients [91]. It can be safely performed with minimal perioperative morbidity and mortality. Better outcomes have been observed in studies with shorter follow-up periods (<3 years) [92].

The following diagnostic methodologies are suggested to be used in NERD patients before the surgery;

1. Upper gastrointestinal endoscopy with biopsies for eosinophilic esophagitis
2. High-resolution esophageal manometry
3. 24 h pH-impedance or wireless capsule pH monitoring study
4. Gastric emptying testing if symptoms are suggestive.

Patients with typical GERD symptoms and good response to PPI give the best results; in case of functional gastrointestinal symptoms, such as bloating, belching and especially without major psychological co-morbidity results are less promising. Partial fundoplication yields better outcome in patients with preoperative major depression. Surgical success is lower in PPI-unresponsive patients and these patient group of patients should be carefully evaluated before surgery with all diagnostic tools as well as psychological evaluation (Fig. 5).

Summary of the therapeutic approach

Lifestyle changes, particularly weight loss and cessation of smoking should be the first line approach in all cases. Different than the animal studies [23], the effects of alcohol consumption on the symptoms are not clear [94]. Diet should be advised according to the symptoms and strict diet restrictions should be avoided. Different guidelines have been proposed (Fig. 6). One management possibility is to divide the patients according to symptom severity at first, followed by evaluation with diagnostic modalities in case of PPI unresponsiveness [95]. In the presence of mild symptoms (less than 3 times a week, minimal impact on quality of life, short duration), on-demand therapy with any effective medication, such as antacids, alginate or antacid/alginate combination, H_2 receptor antagonist and low dose of PPI can be initiated. While patients with moderate symptoms need a single dose and those with severe symptoms need double dose of PPI, it is possible to combine the PPI with prokinetics or alginate, if necessary. In PPI unresponsive patients, further diagnostic modalities, such as high resolution esophageal manometry and 24 h pH-impedance monitoring should be performed [96]. According to the results of these modalities, phenotypes can be diagnosed and managed accordingly.

Within a one-year period, 14–64% of patients can stop PPIs. Different strategies for reducing or stopping PPIs are suggested [97].

1. Abrupt stop
2. Step down and stop slowly
3. Step down and reach the lowest effective dose; continuous therapy
4. Switch to intermittent/on-demand use
5. Stop & switch to other medications (alginate) with continuous or on-demand use

A sudden stop is not advisable because of possible acid rebound problem.

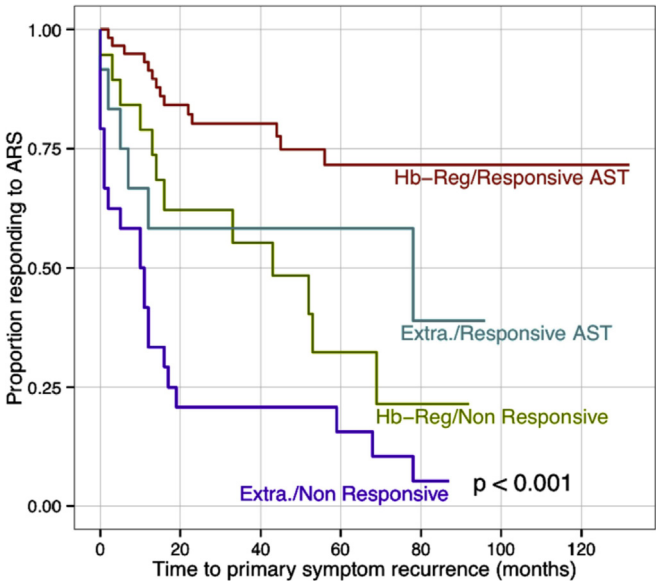

Fig. 5. Time to primary symptom recurrence by primary symptom and preoperative response to acid suppression therapy [93].

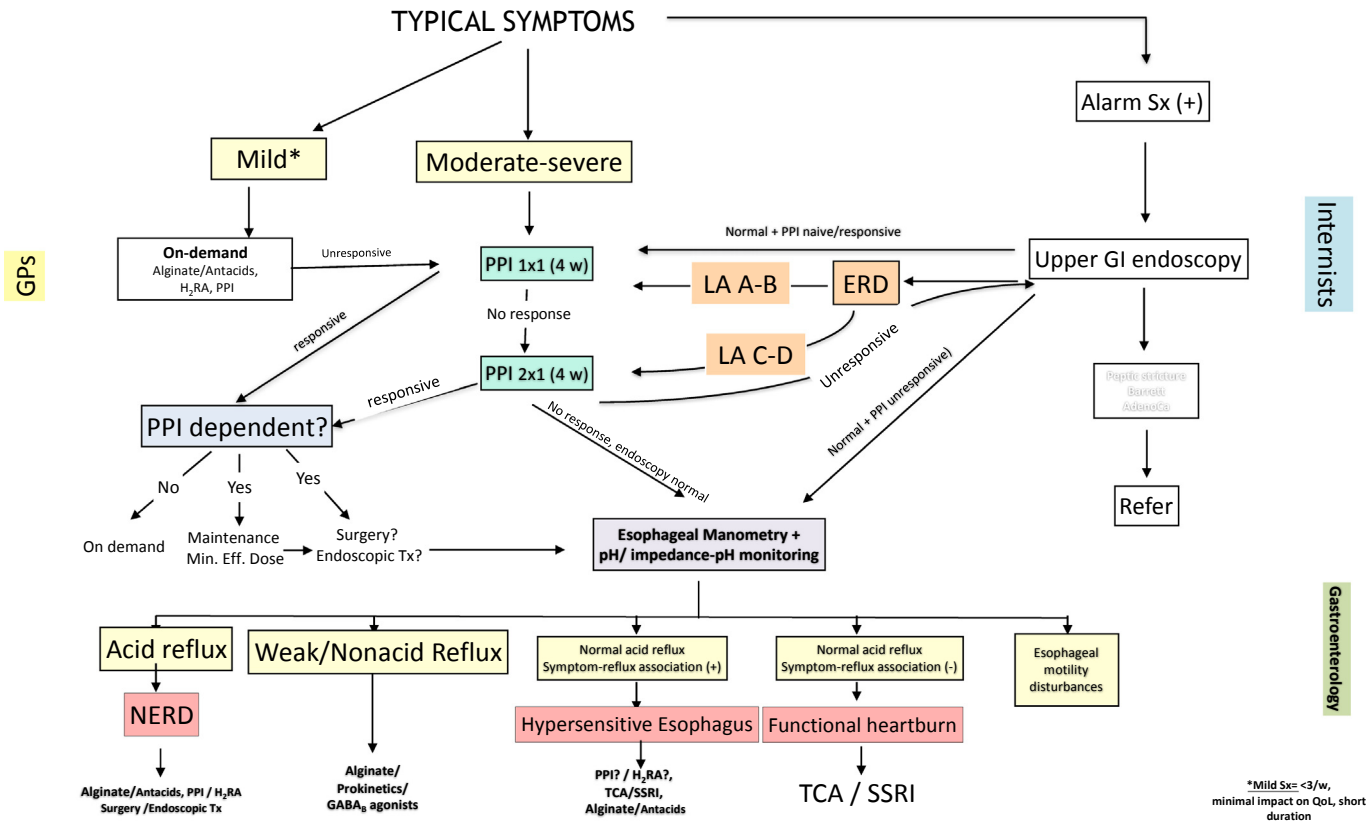

Fig. 6. GERD management algorithm (modified from 95).

Management of reflux hypersensitivity: Reassurance is the first and possibly the most important step of the management protocol. Diagnostic tests and especially upper gastrointestinal endoscopy should not be repeated unless there is a clear-cut indication. It should be remembered that this is a diagnosis based on 24 h pH-MII measurement. First step of the diagnosis is PPI test, and ambulatory measurements are indicated, mainly for PPI unresponsive patients. Almost all the patients who were diagnosed to have reflux hypersensitivity have tried PPI treatment and need some additional approach. The below mentioned empiric approaches can be suggested;

1. Increase the dose of PPI
2. Shift to another brand of PPI?
3. Co-prescription with alginate, prokinetics, neuromodulators including tricyclic antidepressants, SSRIs, serotonin noradrenergic reuptake inhibitors, and gabapentinoids,
4. Antireflux surgery; there are very limited studies showing a good response [98].

Large clinical trials showing the efficacy of these management approaches either alone or with combination are needed.

Management of functional heartburn

There is a debate whether functional heartburn is a part of GERD spectrum or entirely a different entity. This group of patients is under the highest risk of repetitive diagnostic tests, especially upper gastrointestinal endoscopy without any benefit. A strong reassurance from the clinician should be the first step. As mentioned above, psychiatric comorbidity is very common in these patients. A more flexible approach for psychiatric consultation is advisable. Undoubtedly, higher PPI doses or antireflux surgery should be avoided. Otherwise, a similar approach summarized for reflux hypersensitivity should be followed. Neuromodulators should be one of the first approaches unless initiated by psychiatric consultation. Other approaches such as behavioral modification, acupuncture, or relaxation therapy may be beneficial, however convincing data do not exist [3].

Practice points

* GERD is possibly one of the most common chronic diseases in adults in developed countries. However prevalence and symptom profile differs tremendously between Western and Eastern parts of the world.
* The pathogenesis of the disease is complex and multifactorial although initiating or triggering factors are not clearly defined.
* There is an increasing interest for the functional part of the disease however diagnosis and therapeutic approach are particularly limited.
* Proton pump inhibitors are the most widely used medications but should be carefully prescribe with regard to the ineffectiveness on the functional part

Research agenda

* The pathogenetic mechanisms about the initiating factors of the disease and differences of functional vs non-functional phenotypes need to be defined.
* Functional heartburn deserves more attention and decision should be taken whether this is a part of the GERD

* New diagnostic tools for possible differential diagnoses as well as better normative values of current ones need to be clearly defined.
* Associations between psychiatric co-morbidities and GERD phenotypes need more and intensive research.
* More and well-designed studies with neuromodulators are needed to study functional phenotypes out of non-cardiac chest pain

Conflicts of interest

I do not have any conflict of interest regarding this manuscript.

Acknowledgement

I appreciate Roy C. Orlando MD. for his unvaluable mentorship at Tulane University Sect. Gastroenterology during Akdamar Fellowship Program.

References

[1] Bor S. World gastroenterology organization. Heartburn handbook. Worldwide epidemiology of gastroesophageal disease. 2015. p. 12–4. http://www.worldgastroenterology.org/UserFiles/file/WDHD-2015-handbook-final.pdf.
[2] Akyuz F, Mutluay Soyer O. How is gastroesophageal reflux disease classified? Turk J Gastroenterol 2017;28(Suppl 1):S10–1.
[3] Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. Gastroenterology 2016;15. S0016-5085(16)00178-5.
[4] Patti MG, Goldberg HI, Arcerito M, Bortolasi L, Tong J, Way LW. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure and the degree of mucosal injury. Am J Surg 1996;171:182–6.
[5] Welch RW, Luckmann K, Ricks P, Drake ST, Bannayan G, Owensby L. Lower esophageal sphincter pressure in histologic esophagitis. Dig Dis Sci 1980;25:420–6.
[6] Ahtaridis G, Snape WJ, Cohen S. Clinical and manometric findings in benign peptic strictures of the esophagus. Dig Dis Sci 1979;24:858–61.
[7] Roman S, Holloway R, Keller J, Herbella F, Zerbib F, Xiao Y, et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neuro Gastroenterol Motil 2017;29(2).
[8] Klein WA, Parkman HP, Dempsey DT, Fisher RS. Sphicterlike thoracoabdominal high pressure zone after esophagogastrectomy. Gastroenterology 1993;105:1362–9.
[9] Baldi F, Longanesi A, Ferrarini F, Michieletti G, Morselli-Labate AM. Oesophageal motor function and outcome of treatment with H2-blockers in erosive oesophagitis. J Gastrointest Mot (Neurogastroent mot) 1992;4:165–71.
[10] Orlando RC. Reflux esophagitis. In: Yamada T, editor. Textbook of gastroenterology. second ed. Philadelphia: JB Lippincott Company; 1995. p. 1214–42.
[11] Leite LP, Johnston BT, Barrett J, Castell JA, Castell DO. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. Dig Dis Sci 1997;42:1859–65.
[12] Ribolsi M, Balestrieri P, Emerenziani S, Guarino MP, Cicala M. Weak peristalsis with large breaks is associated with higher acid exposure and delayed reflux clearance in the supine position in GERD patients. Am J Gastroenterol 2014;109:46–51.
[13] Skoczylas T, Yandrapu H, Poplawski C, Asadi M, Wallner G, Sarosiek J. Salivary bicarbonate as a major factor in the prevention of upper esophageal mucosal injury in gastroesophageal reflux disease. Dig Dis Sci 2014;59:2411–6.
[14] Yandrapu H, Marcinkiewicz M, Poplawski C, Han K, Zbroch T, Goldin G, et al. Role of saliva in esophageal defense: implications in patients with nonerosive reflux disease. Am J Med Sci 2015;349(5):385–91.
[15] Hirschowitz BI. Gastric secretion of acid and pepsin in patients with esophageal stricture and appropriate controls. Dig Dis Sci 1996;41:2115–22.
[16] Ergun P, Kipcak S, Dettmar PW, Woodcock A, Bor S. Pepsin and pH levels of human gastric juice in gastroesophageal reflux disease and functional heartburn. U Eur Gastroenterol J 2017;5(Supplement 1).
[17] Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal mucosal injury: a review of animal and human studies. Gastroenterology 1995;108:1897–907.
[18] Bor S, Caymaz-Bor C, Tobey NA, Abdulnour-Nakhoul S, Marten E, Orlando RC. Effect of ethanol on the structure and function of rabbit esophageal epithelium. Am J Physiol 1998;274(5 Pt 1):G819–26.
[19] Bor S, Capanoglu D. The additive effect of ethanol and extract of cigarette smoke on rabbit esophagus epithelium. J Gastroenterol Hepatol 2009;24(2):316–21.
[20] Long JD, Marten E, Tobey NA, Orlando RC. Luminal hypertonicity and the susceptibility of rabbit esophagus to acid injury. Dis Esophagus 1998;11(2):94–100.
[21] Tobey NA, Sikka D, Marten E, Caymaz-Bor C, Hosseini SS, Orlando RC. Effect of heat stress on rabbit esophageal epithelium. Am J Physiol 1999;276(6):G1322–30.
[22] Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology 2005;128:771–8.
[23] Bor S, Bor-Caymaz C, Tobey NA, Abdulnour-Nakhoul S, Orlando RC. Esophageal exposure to ethanol increases risk of acid damage in rabbit esophagus. Dig Dis Sci 1999;44(2):290–300.
[24] Orlando RC. Pathophysiology of gastroesophageal reflux disease. J Clin Gastroenterol 2008;42(5):584–8.
[25] Orlando RC. The integrity of the esophageal mucosa. Balance between offensive and defensive mechanisms. Best Pract Res Clin Gastroenterol 2010;24(6):873–82.
[26] Bor S. Acid. In: Johnson N, Toohill RJ, editors. Effects, diagnosis & management of extra-esophageal reflux. Nova Science Publishers Inc.; 2010. p. 19–28.
[27] Tack J, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. Gastroenterology 2018;154(2):277–88.
[28] Fass R, Naliboff B, Higa L, Johnson C, Kodner A, Munakata J, et al. Differential effect of long-term esophageal acid exposure on mechanosensitivity and chemosensitivity in humans. Gastroenterology 1998;115:1363–73.
[29] Patel S, Rao S. Biomechanical and sensory parameters of the human esophagus at four levels. Am J Physiol Gastrointest Liver Physiol 1998;275:G187–91.
[30] Cicala M, Emerenziani S, Caviglia R, Guarino MP, Vavassori P, Ribolsi M, et al. Intraoesophageal distribution and perception of acid reflux in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003;18:605–13.
[31] Souza RF, Huo X, Mittal V, Schuler CM, Carmack SW, Zhang HY, et al. Gastroesophageal reflux might cause esophagitis through a cytokine-mediated mechanism rather than caustic acid injury. Gastroenterology 2009;137:1776–84.
[32] Woodland P, Shen Ooi JL, Grassi F, Nikaki K, Lee C, Evans JA, et al. Superficial esophageal mucosal afferent nerves may contribute to reflux hypersensitivity in nonerosive reflux disease. Gastroenterology 2017;153(5):1230–9.
[33] Lawal A, Kern M, Sanjeevi A, Antonik S, Mepani R, Rittmann T, et al. Neurocognitive processing of esophageal central sensitization in the insula and cingulate gyrus. Am J Physiol Gastrointest Liver Physiol 2008;294(3):G787–94.
[34] Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neuro Gastroenterol Motil 2015;27(9):1202–13.
[35] Phillips ML, Gregory LJ, Cullen S, Coen S, Ng V, Andrew C, et al. The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. Brain 2003;126(Pt 3):669–84.
[36] Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. Gut 2008;57:674–83.
[37] Bilgi MM, Vardar R, Yıldırım E, Veznedaroğlu B, Bor S. Prevalence of psychiatric comorbidity in symptomatic gastroesophageal reflux subgroups. Dig Dis Sci 2017;62(4):984–93.
[38] Bor S, Sarıtaş Yüksel E. How is the gastroesophageal reflux disease prevalence, incidence, and frequency of complications (stricture/esophagitis/Barrett's esophagus/carcinoma) in Turkey compared to other geographical regions globally? Turk J Gastroenterol 2017;28(Suppl 1):S4–9.
[39] Bor S, Lazebnik LB, Kitapcioglu G, Manannikof I, Vasiliev Y. Prevalence of gastroesophageal reflux disease in Moscow. Dis Esophagus 2016;29(2):159–65.
[40] Zentilin P, Marabotto E, Pellegatta G, Coppo C, Furnari M, Savarino E, et al. Complexity and diversity of gastroesophageal reflux disease phenotypes. Minerva Gastroenterol Dietol 2017;63(3):198–204.
[41] Hirano I, Richter JE. Practice Parameters Committee of the American College of Gastroenterology. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol 2007;102(3):668–85.
[42] Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: the Lyon consensus. Gut 2018;67(7):1351–62.
[43] Fass R, Ofman JJ, Sampliner RE, Camargo L, Wendel C, Fennerty MB. The omeprazole test is as sensitive as 24-h oesophageal pH monitoring in diagnosing gastro-oesophageal reflux disease in symptomatic patients with erosive oesophagitis. Aliment Pharmacol Ther 2000;14(4):389–96.
[44] Klauser AG, Schindlbeck NE, Muller-Lissner A. Symptoms in gastro-oesophageal reflux disease. Lancet 1990;335:205–8.
[45] Boeckxstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. Gut 2014;63(7):1185–93.
[46] Vardar R, Keskin M. What is the place of empirical proton pump inhibitor testing in the diagnosis of gastroesophageal reflux disease? (Description, duration, and dosage). Turk J Gastroenterol 2017;28(Suppl 1):S12–5.
[47] Poh CH, Gasiorowska A, Navarro-Rodriguez T, Willis MR, Hargadon D, Noelck N, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointest Endosc 2010;71:28–34.
[48] Roman S, Gyawali CP, Savarino E, Yadlapati R, Zerbib F, Wu J, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. Neuro Gastroenterol Motil 2017;29(10):1–15.
[49] Akdamar K, Ertan A, Agrawal NM, McMahon FG, Ryan J. Upper gastrointestinal

endoscopy in normal asymptomatic volunteers. Gastrointest Endosc 1986;32:78–80.
[50] Naik RD, Vaezi MF. Recent advances in diagnostic testing for gastroesophageal reflux disease. Expert Rev Gastroenterol Hepatol 2017;11(6):531–7.
[51] Jovov B, Que J, Tobey NA, Djukic Z, Hogan BL, Orlando RC. Role of E-cadherin in the pathogenesis of gastroesophageal reflux disease. Am J Gastroenterol 2011;106(6):1039–47.
[52] Bor S, Ergun P, Kipcak S. Biomarkers of reflux disease. Clin Gastroenterol Hepatol 2017;15(2):319–20.
[53] Gupta N, Sharma P. Editorial: novel imaging for endoscopic evaluation of gastroesophageal reflux disease: seeing is believing. Am J Gastroenterol 2012;107(6):875–7.
[54] Reddymasu SC, Sharma P. Advances in endoscopic imaging of the esophagus. Gastroenterol Clin N Am 2008;37(4):763–74.
[55] Park J, Cho YK, Kim JH. Current and future use of esophageal capsule endoscopy. Clin Endosc 2018;51(4):317–22.
[56] Wiener GJ, Morgan TM, Copper JB, Wu WC, Castell DO, Sinclair JW, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci 1988;33:1127–33.
[57] Abdul-Hussein M, Zhang C, Castell D. Symptom index or symptom association probability? A closer look at symptom association in suspected GERD patients. J Clin Gastroenterol 2018;52(1):e7–10.
[58] Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsistency in the diagnosis of functional heartburn: usefulness of prolonged wireless pH monitoring in patients with proton pump inhibitor refractory gastroesophageal reflux disease. J Neurogastroenterol Motil 2015;30:265–72. 21(2).
[59] Gyawali CP, Roman S, Bredenoord AJ, Fox M, Keller J, Pandolfino JE, et al. International GERD Consensus Working Group. Classification of esophageal motor findings in gastro-esophageal reflux disease: conclusions from an international consensus group. Neuro Gastroenterol Motil 2017 Dec;29(12). https://doi.org/10.1111/nmo.13104.
[60] Zhong C, Duan L, Wang K, Xu Z, Ge Y, Yang C, et al. Esophageal intraluminal baseline impedance is associated with severity of acid reflux and epithelial structural abnormalities in patients with gastroesophageal reflux disease. J Gastroenterol 2013;48:601–10.
[61] Frazzoni M, Savarino E, de Bortoli N, Martinucci I, Furnari M, Frazzoni L, et al. Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. Clin Gastroenterol Hepatol 2016;14(1):40–6.
[62] Frazzoni M, Manta R, Mirante VG, Conigliaro R, Frazzoni L, Melotti G. Esophageal chemical clearance is impaired in gastro-esophageal reflux disease–a 24-h impedance-pH monitoring assessment. Neuro Gastroenterol Motil 2013;25(5):399–406.
[63] Holtmann G, Adam B, Liebregts T. Review article: the patient with gastro-oesophageal reflux disease-lifestyle advice and medication. Aliment Pharmacol Ther 2004;20(Suppl 8):24–7.
[64] Sandhu DS, Fass R. Current trends in the management of gastroesophageal reflux disease. Gut and liver, Published online April 24, 2017
[65] Mion F, Dargent J. Gastro-oesophageal reflux disease and obesity: pathogenesis and response to treatment. Best Pract Res Clin Gastroenterol 2014;28(4):611–22.
[66] Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
[67] Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut 2004;53:1730–5.
[68] Ness-Jensen E, Lagergren J. Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. Best Pract Res Clin Gastroenterol 2017;31(5):501–8.
[69] Khan BA, Sodhi JS, Zargar SA, Javid G, Yattoo GN, Shah A, et al. Effect of bed head elevation during sleep in symptomatic patients of nocturnal gastroesophageal reflux. J Gastroenterol Hepatol 2012;27:1078–82.
[70] Bor S, Bayrakci B, Erdogan A, Yildirim E, Vardar R. The influence of the speed of food intake on multichannel impedance in patients with gastro-oesophageal reflux disease. U Eur Gastroenterol J 2013;1:346–50.
[71] Bor S, Bayrakci B, Erdogan A, Yildirim E, Vardar R. The impact of the speed of food intake on intraesophageal reflux events in obese female patients. Dis Esophagus 2017 Jan 1;30(1):1–6.
[72] Koop H. Medical therapy of gastroesophageal reflux disease. In: Granderath Kamolz, Pointner, editors. Gastroesophageal reflux disease; principles of disease, diagnosis, and treatment. Springer Wien Newyork; 2006. p. 103–11.
[73] Tougas G, Armstrong D. Efficacy of H2-receptor antagonists in the treatment of gastroesophageal reflux disease and its symptoms. Can J Gastroenterol 1997;11(suppl B):51–4.
[74] Gyawali CP, Fass R. Management of gastroesophageal reflux disease. Gastroenterology 2018;154:302–18.
[75] Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev 2004;4:CD003245.
[76] Dean BB, Gano Jr AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004;2(8):656–64.
[77] Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? Gut 2012;61:1501–9.
[78] Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW. Impact of regurgitation on health-related quality of life in gastro-oesophageal reflux disease before and after short-term potent acid suppression therapy. Gut 2014;63(5):720–6.
[79] Dettmar PW, Sykes J, Little SL, Bryan J. Rapid onset of effect of sodium alginate on gastro-oesophageal reflux compared with ranitidine and omeprazole, and relationship between symptoms and reflux episodes. Int J Clin Pract 2006;60:275–83.
[80] Lai IR, Wu MS, Lin JT. Prospective, randomized, and active controlled study of the efficacy of alginic acid and antacid in the treatment of patients with endoscopy-negative reflux disease. World J Gastroenterol 2006;12:747–54.
[81] De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ. Gaviscon Double Action Liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. Aliment Pharmacol Ther 2014;40:531–7.
[82] Pouchain D, Bigard MA, Liard F, Childs M, Decaudin A, McVey D. Gaviscon (R) vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. a direct comparative randomised trial. BMC Gastroenterol 2012;12:18.
[83] Hellström PM, Al-Saffar A. Gastroparesis: pharmacotherapy and cardiac risk. Scand J Gastroenterol 2018;53:513–8.
[84] Al-Saffar A, Lennernäs H, Hellström PM. Gastroparesis, metoclopramide, and tardive dyskinesia: risk revisited. Neuro Gastroenterol Motil 2019 May 2:e13617.
[85] Arana A, Johannes CB, McQuay LJ, Varas-Lorenzo C, Fife D, Rothman JK. Risk of out-of-hospital sudden cardiac death in users of domperidone, proton pump inhibitors, or metoclopramide: a population-based nested case-control study. Drug Saf 2015;38:1187–99.
[86] Bor S, Demir M, Ozdemir O, Yuksel K. A meta-analysis on the cardiac safety profile of domperidone compared to metoclopramide. U Eur Gastroenterol J 2018;6(9):1331–46.
[87] Elsborg L, Beck B, Stubgaard M. Effect of sucralfate on gastroesophageal reflux in esophagitis. Hepato-Gastroenterology 1985;32:181–4.
[88] Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, et al. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol 2012;107:1662–7.
[89] Ostovaneh MR, Saeidi B, Hajifathalian K, Farrokhi-Khajeh-Pasha Y, Fotouhi A, Mirbagheri SS, et al. Comparing omeprazole with fluoxetine for treatment of patients with heartburn and normal endoscopy who failed once daily proton pump inhibitors: double-blind placebo-controlled trial. Neuro Gastroenterol Motil 2014 May;26(5):670–8.
[90] Limsrivilai J, Charatcharoenwitthaya P, Pausawasdi N, Leelakusolvong S. Imipramine for treatment of esophageal hypersensitivity and functional heartburn: a randomized placebo-controlled trial. Am J Gastroenterol 2016;111(2):217–24.
[91] Schijven MP, Gisbertz SS, van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. Best Pract Res Clin Gastroenterol 2014;28(1):97–109.
[92] Peters JH. Laparoscopic treatment of gastroesophageal reflux. In: Talamini Mark A, editor. Advanced therapy in minimally invasive surgery. BC Decker Inc; 2006. p. 111–20.
[93] Krill JT, Naik RD, Higginbotham T, Slaughter JC, Holzman MD, Francis DO, et al. Association between response to acid-suppression therapy and efficacy of antireflux surgery in patients with extraesophageal reflux. Clin Gastroenterol Hepatol 2017;15(5):675–81.
[94] Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut 2018;67(3):430–40.
[95] Celebi A, Yilmaz H. What is proton pump inhibitors unresponsiveness in gastroesophageal reflux disease? How should these cases be managed? Turk J Gastroenterol 2017;28(Suppl 1):S71–2.
[96] Ates F, Francis DO, Vaezi MF. Refractory gastroesophageal reflux disease: advances and treatment. Expert Rev Gastroenterol Hepatol 2014;8(6):657–67.
[97] Haastrup P, Paulsen MS, Begtrup LM, Hansen JM, Jarbøl DE. Strategies for discontinuation of proton pump inhibitors: a systematic review. Fam Pract 2014;31(6):625–30.
[98] Broeders JA, Draaisma WA, Bredenoord AJ, de Vries DR, Rijnhart-de Jong HG, Smout AJ. Oesophageal acid hypersensitivity is not a contraindication to Nissen fundoplication. Br J Surg 2009;96(9):1023–30.