REVIEW ARTICLE

REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE: SCOPES BEYOND PPI

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Abstract

Gastroesophageal reflux disease (GERD) is a very common GI disorder where the reflux of gastric contents into the esophagus causes symptom generation. PPI is the principal weapon to fight against GERD. An empiric course of PPI therapy is a cost-effective strategy for managing GERD. But sometimes, PPI can only do so much if taken correctly. As PPI does not reduce the number of reflux, other measures, including lifestyle modification, are required to get relief of GERD symptoms. Most patients respond to 8 weeks of PPI therapy, but 20-40% do not respond or respond partially. While these patients are labeled as having refractory heartburn, many do not have GERD or have not been treated adequately. So, alternative etiology must be considered when patients are refractory to PPI. Endoscopy of upper GIT should be done initially in case of the presence of alarm symptoms and when considered refractory to exclude other conditions. If endoscopy reveals no abnormality, then esophageal function tests like esophageal manometry, 24 hrs ambulatory pH monitoring, and mucosal impedance test can be considered to exclude other related conditions. Endoscopic and surgical treatment options can also be considered in particular cases.

Key words: *Gastroesophageal reflux disease, Refractory GERD, PPI, esophagus*

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Introduction

Gastroesophageal reflux disease (GERD) refers to reflux of gastric contents to the esophagus causing troublesome symptoms (classically heat burn and regurgitation).[1] It is among the most common conditions seen in ambulatory clinics, and its disease burden continues to rise.[2] The highest prevalence of GER symptoms was reported in the Central American study (19.6%) and the lowest in Asia (10.0%), particularly in Southeast Asian countries (7.4%). However, studies from rural Asian communities on the prevalence of GERD are scanty.[3]

The leading inciting agent causing symptoms of GERD is gastric acid, and PPI is the agent that reduces this gastric acid production. Despite that one third of the patients don't respond or partially respond to optimized PPI therapy.[4] However, a substantial group of patients do not comply with prescribed dose and schedule of PPI.

Based on endoscopic findings, GERD can be subdivided into erosive reflux disease (ERD) and non-erosive reflux disease (NERD). In one study, patients with NERD, who comprise up to 70% of the GERD population, had a lower effective response rate to once-daily PPI therapy at four weeks than patients with erosive esophagitis (37% vs 56%, respectively).[5] On the other hand, patients with heartburn do not always have significant gastroesophageal reflux. Patients may have the physiological amount of gastroesophageal reflux but increased response than other normal people (Reflux hyper-sensitivity) or may have no relation of their symptom with their actual reflux event (Functional heartburn).

Methodology:

The information used to write this narrative review was collected from books, online websites, and published papers retrieved from the PubMed database. The literature search was conducted with PubMed for English language

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studies from 2000 to 2021 using the following search terms about GERD ("GERD", "Refractory GERD", "GERD phenotypes", "ambulatory pH", "pH –impedance monitoring", "TLESR", "PPI","non-acidic reflux", "acid pocket", "eosinophilic esophagitis", "reflux hypersensitivity", "functional heartburn"). The bibliographies of the retrieved articles were manually searched for additional relevant studies. Emphasis was given to the selection of randomized controlled trials (RCT), systematic review, meta-analysis, clinical practice guidelines, and large cohort studies.

Refractory GERD:

Refractory GERD is defined by the persistent presence of troublesome GERD symptoms with objective evidence of GERD despite PPI optimization for at least eight weeks [6]. Once refractory GERD is suspected, the underlying cause should be explored. More than two-thirds of the patients referred with refractory heartburn do not have GERD.

Main causes for refractory GERD:

- Insufficient acid suppression-
- Lack of compliance
- Improper dosing time
- Reduced bioavailability of PPIs
- Weakly acidic reflux or non acidic reflux
- Nocturnal acid breakthrough
- Frequent TLESR (transient lower esophageal sphincter relaxation)
- Ineffective Esophageal motility
- Eosinophilic esophagitis
- Reflux hypersensitivity
- Functional heart burn

PPI non-compliance:

PPI plays the most important role in the management of GERD. But, its optimum action depends upon some factors. PPI only selectively interacts with and inhibits actively secreting proton pump. Pre-meal dosing, especially before breakfast, has been proven to most effectively reduce acid secretion.[7] However, a recent survey of 100 GERD patients on PPI found only 46% to be dosing optimally (i.e., within one hour before a meal). In contrast, only 12% dosed in a manner that maximized acid suppression (15–30 min before breakfast).[8] However, patients are not always appropriately instructed about the timing of PPI intake relative to eating.

The difference in PPI metabolism:

PPIs are metabolized mainly through the CYP2C19 hepatic cytochrome system. The activity of CYP2C19 is determined to some extent by a genetic polymorphism. Approximately 5 percent of White patients and >10 percent of Asian patients are homozygous for a *CYP2C19* mutation (i.e., slow metabolizers), potentially leading to more significant gastric acidity suppression. However, in wild-type homozygotes (rapid metabolizers) the effect of PPIs on gastric acidity is diminished and may contribute to PPI failure.[9] So, CYP2C19-independent PPI (i.e., rabeprazole and esomeprazole) can solve PPI failure in rapid metabolizers.

Weakly acidic reflux or non-acidic reflux:

Weakly acidic reflux refers to any reflux event where esophageal pH drops more than one pH unit but remains >4<7. Non-acidic reflux refers to any reflux event where esophageal pH rises above 7.[10] Weakly acidic reflux may arise from partial acid suppression, and non-acidic reflux may occur from duodenogastroesophageal reflux. Proximal migration of weakly acidic reflux and the presence of mixed liquid–gas reflux have increased reflux perception and, thus, symptom generation.[11]

Nocturnal acid breakthrough:

Nocturnal acid secretion, mainly driven by histamine, is less sensitive to PPIs, as evidenced by a nocturnal drop in gastric pH, even in patients on double-dose PPI. This phenomenon is referred to as nocturnal acid breakthrough.[12] It is extremely common, as it is experienced by as many as 80% of patients on twice-daily PPI therapy.[13] H2 blockers help to decrease nocturnal acid breakthroughs. Studies have shown that in patients with double-dose PPI and nightly H2 blockers, nighttime reflux symptoms are improved, and sleep is less disturbed.[14] But due to the development of tolerance to H2 blocker, no benefit is seen if H2 blocker is used for the long term.

Acid pocket:
The concept of acid pocket arises from the observation that reflux episodes are more marked after having a meal. An acid pocket refers to a reservoir of gastric acid floating on top of the meal [15]. This 'acid pocket' of newly secreted gastric juice does not mix with the meal. It can be detected at the esophagogastric junction within 20 minutes after a meal making it a novel target for reducing postprandial heartburn.[16]

Weak anti-reflux barrier:
Lower esophageal sphincter (LES) with crural diaphragm act as a barrier to gastroesophageal reflux. Hypotensive resting LES and/or hiatal hernia cause weakening of anti-reflux barrier and can lead to increased reflux burden and acid exposure.

Frequent TLESR (transient lower esophageal sphincter relaxation):
TLESRs are relaxations of the lower esophageal sphincter (LES) accompanied by inhibition of the crural diaphragm. TLESR is physiological but in reflux disease, this number of TLESR is markedly increased. It is considered the main underlying mechanism for gastroesophageal reflux in most GERD patients (55–80%), particularly in patients with NERD.[17]

Ineffective Esophageal motility:
Reduced esophageal clearance of refluxate occurs in the setting of an esophageal motility disorder, including achalasia. This causes prolonged exposure of the esophageal mucosa to toxic refluxate components and thereby causes significant symptoms.

Eosinophilic esophagitis:
Eosinophilic esophagitis is a very important but less recognized clinical condition in the setting of refractory heart burn. Although some patients with eosinophilic esophagitis respond to PPI (PPI responsive esophageal eosinophilia, PPI-REE), most patients require proper diagnosis and additional treatment.[18]

Esophageal hypersensitivity:
Reflux hypersensitivity is characterized by retrosternal symptoms, including heartburn and chest pain associated with non-pathologic acid exposure.[20] There should be no structural changes in the esophagus. In patients with esophageal hypersensitivity, proximal migration of weakly acidic reflux and gas in the refluxate are pivotal for symptom generation.[19,21]

Functional heartburn:
Functional heartburn is defined as retrosternal burning discomfort or pain refractory to acid-suppressive therapy in the absence of gastroesophageal reflux disease. These patients have symptoms similar to typical GERD without any correlation with their true reflux. Patients may have symptoms even in the absence of physiological reflux. It is estimated that up to 58 percent of patients with persistent heartburn, despite PPI therapy, have functional heartburn.[22]

Evaluation:
In patients with heartburn or typical GERD symptoms, PPI can be given directly without any investigation. But if there are any alarm features or in patients with symptoms refractory to PPI, further evaluation is essential to exclude other differentials or complications of GERD.

Upper GI endoscopy:
Upper GI endoscopy may be normal in as many as 70 % of patients with reflux esophagitis (NERD). Endoscopy may reveal esophagitis, complications of GERD, namely Barrett's esophagus, stricture, or malignancy. It may also reveal dilated esophagus as in achalasia, narrow esophageal caliber, mucosal furrowing in eosinophilic esophagitis, and also a hiatus hernia. American College of Gastroenterology (ACG) recommends esophageal biopsy in every patient with refractory GERD to exclude eosinophilic esophagitis.[23]

Reflux testing:
Ambulatory esophageal 24 hours pH monitoring is the gold standard for diagnosing GERD that can be performed by pH-only catheter, multichannel intraluminal impedance-pH (MII-pH) catheter or wireless capsule. In addition to pH monitoring, MII-pH can measure the impedance of esophageal content that passes between two sensing rings. Thus, MII-pH can detect reflux at all pH levels (acidic, weakly acidic, or non-acidic), determine the

characteristics of the content (gas, liquid, or both), and detect the direction of movement (swallow or reflux).[24] It is performed 'off PPI' therapy in unproven GERD patients and 'on PPI' therapy in previously diagnosed cases of GERD but refractory to PPI therapy.[4] In addition to diagnosing true GERD, MII-pH can efficiently differentiate reflux hypersensitivity and functional heartburn.

High-resolution esophageal manometry:
Esophageal manometry has no specific findings for diagnosing GERD. Still, it is helpful to determine the correct positioning for pH catheter placement and to detect the rare case in which achalasia is misdiagnosed as GERD. It can also diagnose underlying causes for GERD like ineffective esophageal motility, hypotensive LES, TLESR. Belching and rumination syndrome, which often cause confusion with GERD, can also be diagnosed by esophageal manometry.[4]

Mucosal impedance testing (MIT):
Though MII-pH (multichannel intraluminal impedance-pH) is considered the gold standard for diagnosing GERD, it has some limitations. It only detects reflux activity during the testing period rather than the long-term mucosal consequences of GERD. Another limitation of MII-pH is that the baseline values in patients with severe erosive esophagitis and Barrett's esophagus are too low to provide accurate results [24]. Mucosal impedance testing (MIT) can overcome these drawbacks of reflux testing. It can be used to assess PPI refractory GERD, differentiate between NERD and function heartburn, and determine GERD from eosinophilic esophagitis.[24]

Table-I
Esophageal test result in GERD assessment.

Diagnosis	Upper GI endoscopy	Reflux monit oring	Mucosal impedance	Response to PPI	Esophageal HRM
GERD	LA grade C/D esophagitis, Peptic stricture, Barrett's esophagus	AET >6%	Low impedance at lower esophagus	Highly responsive	-
True NERD	Normal	AET >6%	Low impedance at lower esophagus	High-intermediate	-
Reflux hypersensitivity	Normal	AET <4%, SI>50%, SAP >95%	normal	Intermediate	-
Functional heart burn	Normal	AET <4%, SI<50%, SAP<95%	normal	Low	-
Inconclusive result	LA grade A/B esophagitis, microscopic inflammation at biopsy	AET 4-6% Number of refluxes >80/ 24 hrs	-		EGJ type -III, Esophageal hypomotility
Result against reflux	-	AET <4% Number of refluxes <40/24 hrs	normal	Low	Achalasia, EGJ outflow obstruction
Eosinophilic esophagitis	Mucosal ring, furrowing, exudate. Eosinophilic infiltration at biopsy >15/HPF	-	Low impedance throughout the esophagus	Some cases are responsive (PPI-REE)	-

AET- acid exposure time, LA- Los Angles classification, SI- symptom index, SAP- symptom association probability, EGJ- esophago-gastric junction, PPIREE- PPI responsive eosinophilic esophagitis. Adapted from Ghisa M, et al. Journal of Neurogastroenterology and Motility. 2020.

Management:

Lifestyle modification:

PPI doesn't reduce the number of reflux. Attempts should be taken to reduce the number of reflux by any means. Some changes in lifestyle significantly reduce symptom occurrence-

- Weight reduction for patients who are overweight or have had recent weight gain.
- Avoidance of dietary items that worsen symptoms – fatty food, alcohol, peppermint, tomato-based food, tea-coffee, acidic food, and carbonated beverages.
- Elevation of the head end of the bed in patients with nocturnal symptoms.
- Avoidance of late meals. Sleeping at least 2 hours after a meal.
- Cessation of smoking and alcohol (as they reduce LES pressure)**.[6]**

Compliance and Adherence:

Studies have demonstrated that up to 50% of patients with heartburn are non-compliant with PPI [25]. As GERD is a symptom-driven disease, compliance may depend on the presence of symptoms. Poor adherence to proper PPI administration time has also been commonly observed in GERD patients, primarily because of a lack of detailed instructions by the prescribing physicians [26]. PPIs only selectively interact with and inhibit actively secreting proton pumps. Hence, pre-meal dosing, especially 30 minutes before breakfast, has been proven to reduce acid secretion most effectively.[27]

Optimization of PPI therapy:

In patients with reflux symptoms despite a standard dose of once-daily PPI, doubling the dose of PPI for eight weeks may be considered before switching to another PPI. In one study, doubling the PPI dose in patients with symptomatic GERD, despite once-daily PPI therapy, increased the rate of overall symptom improvement by 22 to 26 percent [28]. Using CYP2C19-independent PPI (i.e., rabeprazole and esomeprazole) in rapid metabolizers can increase acid suppression, improve symptom response, and improve rates of healing and remission of erosive esophagitis.[9] Therefore, switching therapy from CYP-dependent PPIs to more CYP-independent PPIs in partial PPI responders may be considered. After eight weeks of PPI therapy, if the patient's symptoms improve, the dose of PPI may be tapered to the lowest possible dose**.[25]**

Addition of H2 receptor blocker:

For patients with nighttime symptoms, even after getting a double dose of PPI, an H2 receptor blocker can be added before sleep. They selectively inhibit histamine-driven acid secretion that predominantly occurs at night.[14] However, the effect of the H2 receptor blocker waned if it is used for > 1 month due to tachyphylaxis.[15]

Potassium competitive acid blocker (P-CAB):

Potassium-competitive acid blockers (P-CABs), such as vonoprazan, competitively inhibit both active and inactive proton pumps in contrast to conventional PPI. It requires no prior activation and is stable in acidic conditions. So, it can be taken anytime – before or after a meal. P-CAB concentration in the parietal cells' canaliculi is 100.000-fold higher than in the plasma as compared with PPIs, which are only 1000-fold higher. So, P-CABs have a higher potency and longer duration of action.[29] That's why P-CAB can be tried in patients with partial PPI responder. However, P-CABs are not available in most of countries.

Prokinetics:

Prokinetics are thought to work by reducing the reflux of duodenal juice into the esophagus and speeding the absorption of PPI. In addition, mosapride improves esophageal motility, whereas metoclopramide and domperidone do not have this ability.[30] Mosapride shortens bolus transit time in the esophagus, reduces the duration of the most extended reflux episode, and enhances the contraction strength in the lower esophagus.

TLESR reducer:

GABA-agonists, such as Baclofen, have been shown to decrease the number of TLESR events and reduce heartburn and regurgitation symptoms in PPI refractory GERD compared to placebo.[31] In a meta-analysis of nine

randomized trials that included 283 patients with GERD and healthy volunteers who were assigned to Baclofen or placebo, Baclofen resulted in a reduction in the number of reflux episodes per patient, the average length of reflux episodes, and the incidence of transient lower esophageal sphincter relaxation.[32]

Raft forming agent:

Raft-forming agents (e.g., Alginate) are used to target the acid pocket that is formed after a meal. Alginate forms a floating raft in the presence of acid and calcium ions. This raft potentially creates a physical barrier against reflux or increases the viscosity of refluxate, potentially impeding gastroesophageal reflux.[33] The low side effect profile and unique mechanism of action make Alginate a helpful adjunct to partial PPI response.[34]

Neuromodulators:

Neuromodulators reduce pain sensitivity /pain threshold at the central nervous system and/ or sensory afferents level. They are mainly used in reflux hypersensitivity and functional heartburn, where PPI is usually less/ineffective. Sometimes, there is an overlap of true reflux esophagitis and functional heartburn where PPI and neuromodulators can be used combined. Both tricyclic antidepressants and serotonin reuptake inhibitors can be used as neuromodulators.[35]

Non-pharmacological Approaches

Psychotherapy, acupuncture, and hypnosis may also be beneficial in treating functional heartburn, although very few studies support their role in functional heartburn.[36]

Endoscopic therapy for GERD:

Several endoscopic procedures can be offered to patients with GERD. Candidates for endoscopic therapy are those who exhibit typical symptoms of GERD, such as heartburn and regurgitation, and

- have low-grade erosive esophagitis (Los Angeles Grades A and B),
- endoscopy negative with abnormal esophageal acid exposure,
- a hiatal hernia smaller than 3 cm in size and at least a partial response to PPI treatment.[29]
- patients with poor compliance with medical therapy,
- a desire to discontinue medical treatment, or a preference for nonmedical, nonsurgical therapy.

Transoral Incisionless Fundoplication (EsophyX procedure) —This endoluminal procedure aims to reduce hiatal hernia size, restore the physical barrier of the LES, and prevent reflux of gastric contents [37]. The procedure reinforces the gastroesophageal junction by plicating the upper portion of the stomach (fundus) around the gastroesophageal junction by approximately 270 degrees and securing it with special fasteners**.**[38]

EndoStim® LES Electrical Stimulation System: The Endostim Implantable Device (Endostim Inc.) for the lower esophageal sphincter (LES) functions like a cardiac pacemaker. Bipolar stitch electrodes are laparoscopically placed in the LES and connected to an implantable pulse generator implanted subcutaneously in the anterior abdominal wall**.**[39]

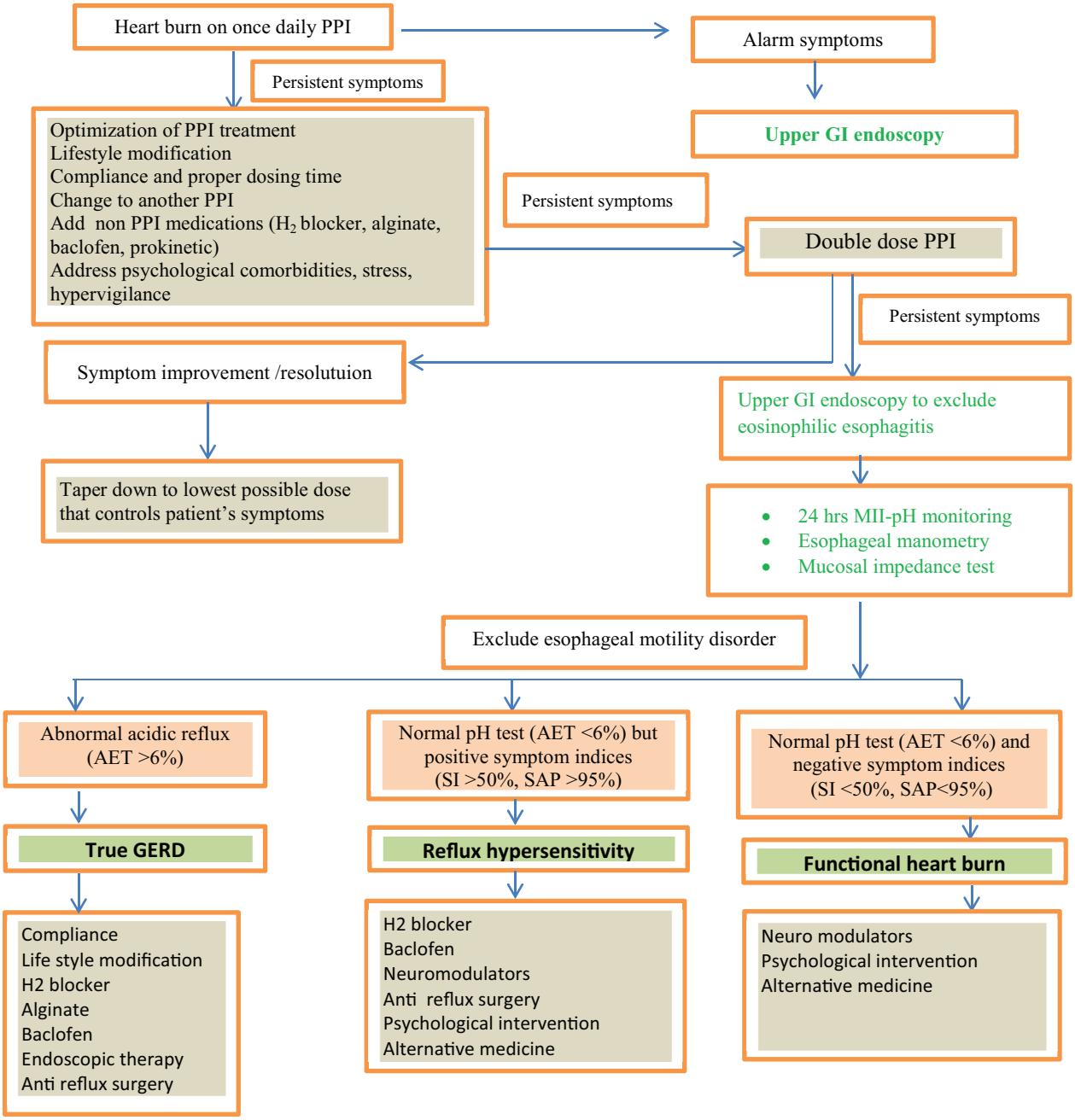
PMMA Microspheres/Collagen Permanent Injectable Bulking Agent

G125 is an experimental permanent injectable bulking agent to treat GERD**.**[40] The combination material consists of uniformly round and smooth polymethylmethacrylate (PMMA) microspheres (125 ìm), evenly suspended in a collagen 'carrier' to achieve permanent and strictly submucosal LES soft tissue augmentation via tissue bulking through a 23G needle. It is considered one of the safest biomaterials for human use, and its excellent biocompatibility and lack of toxicity has been documented in many studies since 1940**.**[41]

Radiofrequency Energy Delivery to the LES (Stretta procedure): It is another minimally invasive treatment with a low adverse event rate (<1%). Radiofrequency energy is delivered through endoscopy to the LES. Studies have shown a significant improvement in symptoms and decreased PPI use with the Stretta procedure.[42]

Surgical therapy for GERD:

Laparoscopic Fundoplication—Laparoscopic fundoplication involves hernia repair with



AET- Acid exposure time, SI- symptom index, SAP- symptom association probability. Adapted from Gyawali CP, et al. Gastroenterology. 2018.

Fig.-2: *Management algorithm for management of refractory heart burn.*

repositioning of the LES in the intra-abdominal cavity and the creation of a one-way flap valve in order to reduce reflux events.[43] Success rates of laparoscopic fundoplication range from 67% to 95% and are highly dependent on surgical expertise, adequate preoperative evaluation, and appropriate patient selection.[44] Three types of fundoplication are commonly practiced-

- Nissen fundoplication- total 3600 fundoplication- may cause post-operative dysphagia in Patients with esophageal poor peristaltic reserve.

- Toupet fundoplication- 270-degree posterior fundoplication
- Dor fundoplication- 180-degree anterior fundoplication

The durability of fundoplication may weaken over time resulting in hiatal herniation proximal to the wrap and/or slippage of the fundoplication.[45]. Up to 30% of patients will develop a prolonged structural complication following fundoplication. Additionally, symptoms such as gas-bloat syndrome, chest pain, and diarrhea following fundoplication are common.[46]

Magnetic Sphincter Augmentation: A 'bracelet' of interlinked magnetic titanium beads (LINX device) is placed endoscopically around the LES to augment EGJ pressure through magnetic attraction. This procedure's most common side effect is dysphagia, and the rate of device migration and esophageal erosion is approximately 0.15%.[47]

Roux-en-Y Gastric Bypass: Obesity is a major risk factor for failure of laparoscopic fundoplication, and procedures such as Roux-en-Y gastric bypass have been studied to treat GERD and obesity. At three year follow-up of 55 patients with morbid obesity undergoing Roux-en-Y gastric bypass, reflux symptoms improved and the incidence of esophagitis decreased.[48] Thus, in morbid obesity, obesity with related comorbidity, or fundoplication failure, Roux-en-Y gastric bypass may be considered for PPI refractory GERD.

Conclusion:

Gastroesophageal reflux disease is a multifactorial GI disorder where hyperacidity is the major but constitutes only one component. PPI only reduces (completely/ partially) acid secretion and doesn't reduce the number of reflux also. In the patient with GERD refractory to PPI, poor compliance, and non-adherence to treatment, the presence of a rapid metabolizer should be kept in mind. Lifestyle modification, the addition of pharmacological agents, in addition to PPI, should be considered in patients with refractory GERD. Reflux hypersensitivity and functional heartburn are frequent and important differential diagnoses for refractory GERD. So, 24 hrs esophageal reflux monitoring, esophageal manometry, and mucosal impedance test should be considered in these patients next to upper GI endoscopy. Endoscopic therapy and surgical therapy can be considered in patients with refractory GERD only after the exclusion of other conditions that cause similar symptoms and after the failure of medical treatment. These procedures also have some effects that sometimes make life miserable.

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