Investigations and Treatment of PPI Refractory GERD

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Abstract

Gastroesophageal reflux disease (GERD) is a common gastrointestinal condition worldwide. Although not life threatening, it affects quality of life and health-care utilization. Most GERD patients are treated in primary care, until medical therapy fails, when a referral to a specialist, usually a gastroenterologist, occurs. Depending on the presenting symptoms and response to medical therapy, the causes of treatment failure can be GERD related or non-GERD related. Endoscopy, pH monitoring, and impedance pH monitoring are the investigations currently used for evaluation of proton pump inhibitor (PPI) refractory GERD. This review attempts to present an account of the current investigations, treatment, and the clinical context for which they are to be used.

Keywords

GERD • NERD • PPI therapy • Barrett's esophagus • PPI failure • Refractory GERD

Introduction

Gastroesophageal reflux disease (GERD) is a common condition affecting 10–20% of the population in the developed world and is increasingly common in Asia and other developing countries. Since their introduction for the treatment of GERD two decades ago, proton pump inhibitors (PPIs) have been shown in numerous clinical trials to be the most effective form of medical treatment. Most, if not all guidelines, recommend their use as the treatment of choice for GERD patients. PPIs are

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effective in symptom relief and healing of mucosal lesions. Despite their high degree of efficacy, failure in patient response to PPIs does occur. About 32% of patients diagnosed with GERD in primary care are reported to be refractory to PPIs. With the increasing use of PPIs as first-line therapy, PPI failure is expected to rise substantially. PPI failure has become a common clinical challenge for primary care providers and specialists.

In a post hoc analysis of the 2007 National Health and Wellness Survey (NHWS) carried out in the USA and Europe, GERD patients with persistent, intense symptoms despite proton pump therapy have a poorer health-related quality of life (HRQOL), lower work productivity, and higher absenteeism than patients with low symptom load. In addition, US respondents with persistent, intense symptoms reported more emergency room visits. A systematic review of 19 studies by Tack concluded disruptive GERD patients had 2.4 times higher mean rates of absenteeism, 1.5 times higher mean rates of presenteeism, 1.5 times lower sleep quality scores, and 1.3 times lower mean scores for psychological and general well-being. Thus, failure to respond to PPI in GERD patients impacts quality of life and increases health-care utilization.

Definition of PPI Failure (Refractory GERD)

There is currently no universally accepted definition of PPI failure. One proposed definition of PPI failure is 50% or less improvement in the chief complaint after at least 12 weeks of PPI therapy [1]. There are difficulties applying this definition in clinical practice, as this is patient-driven based on their expectations.

PPI Failure and GERD Phenotypes

GERD has been divided into three phenotypes by Fass [2]:

1. Nonerosive reflux disease (NERD) comprising 60–70% of GERD cases
2. Erosive esophagitis comprising 20–30%
3. Barrett's esophagus and other complications, about 6–10% of GERD

The Montreal definition and classification of GERD [3] added another group (very extraesophageal GERD syndromes) made up of conditions characterized by symptoms with established or proposed association with GERD. The exact prevalence of these syndromes is difficult to ascertain because the symptoms are nonspecific and the relationship with GERD requires investigations.

These three phenotypes of typical GERD exist separately and mostly remain in the same phenotype over time. Natural history studies demonstrate that 85–90% of NERD patients do not progress to develop erosive esophagitis or Barrett's esophagus. Likewise, patients with erosive esophagitis are unlikely to progress to Barrett's esophagus. Profiling the phenotype that contributes to the growing pool of PPI

refractory, GERD patients will allow development of diagnostic techniques and therapy.

Reflux-Related Causes of PPI Failure

- Compliance
- Improper dosing
- Residual acid reflux
- Non-acid or weakly acidic reflux
- Acid pocket
- Duodenogastric reflux
- Esophageal hypersensitivity
- Concomitant functional disorder including overlap syndromes
- Psychological comorbidity
- Nocturnal acid breakthrough
- PPI metabolism and CYP2C19 polymorphism

Erosive Esophagitis and PPI Failure

Clinical studies in patients with erosive esophagitis have demonstrated 88–96% [4] healing rates following 8 weeks of PPI therapy. Despite healing of mucosal lesions, up to 15% of patients with erosive esophagitis continue to experience GERD symptoms. Erosive esophagitis constitutes less than 30% of patients, who are PPI refractory.

Barrett's Esophagus and PPI Failure

The prevalence of Barrett's esophagus is 6–12% of all GERD patients [4] who are endoscoped and about 0.25–3.9% in all patients undergoing upper GI endoscopy. Symptom relief in patients with Barrett's esophagus is about 80%, although abnormal acid exposure can be demonstrated in 20–40% of patients. With higher-dose PPIs, complete heartburn resolution occurs symptomatic in 80–85% [4] of patients with Barrett's esophagus; thus, 15–20% of patients with Barrett's esophagus are refractory to PPI.

Nonerosive Reflux Disease (NERD) and PPI Failure

As 70% of patients with typical symptoms in a primary care setting do not have mucosal injury, they are diagnosed as NERD. In a systematic review of the literature, PPI symptom response pooled rate was as low as 36.7% in NERD [4] patients. Therefore, most of the PPI refractory patients are likely to come from NERD. It has been shown that esophageal acid exposure and symptoms resolution are directly

related. The greater the esophageal acid exposure, the higher the response rate. Thus it is useful to subdivide NERD patients according to the esophageal acid exposure and their response to PPI. The subtypes are:

1. *Nonerosive reflux disease (NERD)*. These patients have normal endoscopy but abnormal esophageal acid exposure on pH studies. The response to standard dose of PPI is better than the other two subtypes described below.
2. *Hypersensitive esophagus*. At endoscopy these patients have normal endoscopy, normal acid exposure on pH monitoring, but positive symptom-reflux association (symptom index: SI > 50%, SAP > 95%). These patients have a limited response to standard-dose PPIs but show improvement when higher doses are used.
3. *Functional heartburn*. These patients have at endoscopy normal endoscopy mucosa, normal acid exposure, and negative symptom-reflux association. They rarely respond to PPIs.

Non-cardiac Chest Pain (NCCP) and PPI Failure

In the Montreal classification of GERD, non-cardiac chest pain was classified under symptomatic esophageal syndrome. The response of NCCP to PPI was reported in 68 studies, [5] of which three studies were double-blind, placebo controlled involving treatment with PPIs for 4–8 weeks. Two studies showed significant response to PPI (81%, 33%), and the placebo response rate was 6% and 25%, respectively. PPI refractory NCCP could be an important clinical issue in some regions.

Extraesophageal Syndromes and PPI Failure

The Montreal classification introduced the concept of extraesophageal syndromes that have an established or a proposed association with GERD. Although there are epidemiologic and physiologic evidence for an association, there is insufficient evidence to show causality. The extraesophageal syndromes are (1) reflux cough syndrome, (2) reflux laryngitis syndrome, (3) reflux asthma syndrome, and (4) dental erosion syndrome. A therapeutic benefit for acid-suppressive therapy in patients with extraesophageal syndromes such as chronic cough could not be dismissed, but evidence suggests that rigorous patient selection is required to identify patients most likely to respond [6]. The proportion of patients with extraesophageal syndromes who are refractory to PPI is not well documented.

Mechanisms of PPI Failure

Broadly speaking, the factors that could contribute to GERD symptoms despite PPI therapy would fall into two categories:

1. Non-reflux-related causes
2. Reflux-related causes

Non-reflux-Related Causes of PPI Failure

The non-reflux-related causes of refractory GERD include esophageal motility disorders such as impaired gastric emptying and outlet obstruction due to pyloric stenosis or gastric tumor.

Pill esophagitis is caused by medicinal pills that dissolve in the esophagus rather than passing rapidly into the stomach. Common drugs that cause pill esophagitis are antibiotics—especially the newer tetracyclines—bisphosphonates, iron supplements, NSAIDs, and aspirin. Patients with eosinophilic esophagitis usually present with dysphagia, with only about one-third of patients reporting typical heartburn. Prevalence of eosinophilic esophagitis in patients with heartburn ranged between 0.9 and 8.8%. At endoscopy, ridges, farrows, rings, or even multiple rings can be seen. Presence of white exudates is suggestive of eosinophilic esophagitis. Histologically, eosinophilic inflammation is present. At least 15 eosinophils per high-power field are required for diagnosis. Patients with eosinophilic esophagitis may respond to PPIs [7].

Non-reflux-Related Causes of PPI Failure

1. Esophageal motility disorders: e.g., achalasia, scleroderma
2. Other non-reflux-related esophagitis: pill esophagitis, eosinophilic esophagitis, and infectious esophagitis
3. Functional chest pain
4. Functional heartburn
5. Other causes of chronic cough hoarseness
6. Impaired gastric emptying

Functional Heartburn

Functional heartburn is a diagnosis by exclusion based on functional testing and normal endoscopy. It is a distinct entity from NERD and is a common cause for PPI failure in patients with reflux symptoms. Using impedance pH monitoring and a dyspepsia questionnaire, a study demonstrated that there was an increased prevalence of dyspeptic symptoms in patients with functional heartburn and suggested that functional heartburn has more in common with functional dyspepsia than with NERD [8].

Reflux-Related Causes of PPI Failure

Compliance and Improper Dosing

Poor compliance is common in patients with GERD. After 1 month of therapy, only about 55% of GERD patients continued their PPI as instructed by their physician [9]. PPIs should be taken 30 min before breakfast and dinner to achieve maximum acid inhibition. Patients, however, take PPIs incorrectly, and a study found 39% of patients took the PPI at bedtime instead. There is no direct evidence that strict adherence to dosing schedule can improve symptoms.

Residual Acid Reflux

Residual acid reflux has been demonstrated in patients with persistent heartburn despite taking PPIs once or twice daily. In a recent study, Karamanolis demonstrated that 16% and 32% of symptomatic patients on double-dose and standard-dose PPIs, respectively, have abnormal pH tests [10]. Positive symptom index (SI) with an acid reflux event was seen in 40% of patients who were deemed PPI failures on PPIs once daily [11].

Weakly Acidic or Non-acid Reflux

Non-acid gastroesophageal reflux refers to refluxates with pH > 4 and was demonstrated on multichannel intraluminal impedance (MII) with pH sensor. The first postprandial impedance pH study in patients on PPI twice daily documented most of the reflux events were non-acidic. Non-acidic reflux was associated with typical heartburn, although less often than acidic reflux. Other symptoms such as regurgitation and sour or bitter taste in mouth were also associated with non-acid reflux.

Acid Pocket

Non-acid reflux episodes and heartburn occur during the postprandial period. This observation appears contradictory, as intragastric pH is highest (least acidic), following a meal due to the buffering effect of food. In 2001, Fletcher carried out a series of experiments using stepwise pull-through of a pH electrode from proximal stomach into the esophagus in healthy volunteers after a high-fat meal. The investigation detected an area of unbuffered, highly acidic gastric juice at the esophagogastric junction that escapes the buffering effect of a meal. This area of high activity detected in the proximal stomach after a meal is termed acid pocket. Acid pocket can be found in healthy patients as well as in GERD patients and serves as a reservoir for acid reflux. In GERD patients, the acid pocket has a tendency toward upward migration. In the presence of a hiatus hernia, the acid pocket is in a

supradiaphragmatic position, and the propensity for acid reflux is further increased. A recent study demonstrated that after PPI treatment, the acid pocket remained but became smaller and less acidic, and pH increased from 1 to 4. Further research into the acid pocket would be needed to elucidate its role in PPI refractory GERD.

Esophageal Hypersensitivity

Patients with persistent reflux symptoms despite PPI therapy may have normal esophagus acid exposure and normal endoscopy but a positive correlation between symptoms and acid and non-acid reflux events. This is analogous to the visceral hyperalgesia that is seen in other functional gastrointestinal disorders.

Nocturnal Acid Breakthrough (NAB)

Nocturnal acid breakthrough was initially proposed as a major cause of refractory GERD. However, later studies have shown that 70% of patients with refractory GERD experienced NAB, but only in 36% was there a correlation between reflux symptoms and NAB.

Bile Acid Reflux

Early studies suggested that 10–15% of non-acid reflux could be caused by bile reflux. More recent studies, however, demonstrate that most bile reflux occurred with acid reflux, and acid suppression does not guarantee elimination of bile reflux. In a study that included 65 patients with persistent reflux symptoms while on PPI, a number of bile reflux events and symptoms were correlated, suggesting a role for bile reflux.

Impaired Gastric Emptying

Patients who have impaired gastric emptying are predisposed to reflux. Examples are peptic ulcer or gastric tumor causing gastric outlet obstruction.

Psychological Comorbidity

Patients with GERD demonstrate significantly higher anxiety and depression scores when compared with normal subjects. Psychological comorbidity in GERD has been shown to predict the occurrence of GERD-related symptoms regardless of mucosal injury. In our own study in Asia, we found a significantly higher prevalence of minor psychiatric comorbidities in NERD patients (46.7%) and patients with

erosive esophagitis (26.4%) compared with 16.8% in the general population [12]. Patients with non-cardiac chest pain, nutcracker esophagus show a tendency to be hypochondriac and seek medical care early. Thus psychological comorbidity is common among GERD patients and appears to affect all GERD phenotypes. Some patients with GERD do report that their reflux symptoms are triggered by or aggravated during stressful periods.

Concomitant Functional Gastrointestinal Disease

Patients with GERD frequently report dyspeptic symptoms such as nausea, vomiting, early satiety, bloating, and belching. In a recent systematic review, it was found that 38% of GERD patients have dyspeptic symptoms [13]. Patients with NERD had a higher percentage of dyspeptic symptoms compared with erosive GERD patients and had a lower response rate of response with PPIs. This group of patients will require treatment for dyspepsia. Another recent study reported that functional dyspepsia and irritable bowel syndrome are strongly associated with PPI failure in patients with GERD diagnosed on impedance pH studies.

Diagnostic Evaluation

History and Physical Examination

1. Check for non-GERD-related causes, particularly in extraesophageal syndrome.
2. Check drug history for pill esophagitis and other non-GERD-related causes, and check body weight and BMI.
3. Differentiate from functional disorders. The bothersome symptom(s) that is persistent despite PPI therapy should be carefully evaluated. Epigastric burning and heartburn are two symptoms which can be misinterpreted. Epigastric burning is, according to Rome III definition, a feature of dyspepsia and does not have a cephalad retrosternal radiation. By careful history taking, it is possible to detect functional GI disorders. Check for alarm symptoms.
4. Symptoms such as dysphagia, odynophagia, weight loss, anorexia, or upper GI bleeding are red flags for structural disorders. On the other hand, the absence of alarm symptoms should not lead the clinician to complacency.
5. Check the time that the persistent troublesome symptoms occur. This information will help to determine if nocturnal acid breakthrough or acid pocket could be the mechanism for PPI failure.
6. Check for proper dosing and correct timing of PPIs. This should be done before embarking on further investigations and can be improved through patient education.
7. Check for psychological morbidity. Stress can aggravate reflux symptoms and negatively affect the response to PPI.

In patients without alarm symptoms, increasing the dose of a PPI or switching to a different PPI before initiating diagnostic testing can be considered. A randomized controlled trial in patients with persistent GERD symptoms taking a single daily dose of PPI showed that increasing PPI to twice daily or switching to another PPI resulted in symptomatic improvement in about 20% of patients.

Upper GI Endoscopy

Patients who fail to respond either completely or partially to PPIs despite optimization of PPI therapy require further diagnostic workup. Those with typical esophageal symptoms should undergo endoscopy.

When an upper GI endoscopy and biopsy are performed, there is some evidence that dilated intercellular spaces (DIS) may help to differentiate NERD from functional heartburn. Our group has also reported usefulness of narrowband imaging to diagnose GERD [14]. In patients suspected of suffering from eosinophilic esophagitis, esophageal biopsy should be obtained. Obtaining esophageal biopsy in patients with refractory GERD to diagnose eosinophilic esophagitis is cost-effective only when the prevalence of eosinophilic esophagitis is more than 8%, according to a Markov model analysis [15].

An observational study was performed to compare the endoscopic findings in patients who failed to obtain complete or partial response to 8 weeks of once-daily PPI treatment versus patients with reflux symptoms who received no treatment. GERD-related findings were significantly less common in the PPI-treated group compared with those who had not received treatment. Barrett's esophagus was found in about 3% of patients in both groups. Non-GERD-related findings were eosinophilic esophagitis (0.9%), achalasia (0.95%), gastric ulcer (0.95%), gastric/duodenal polyps (10.5% vs 6.6%), gastric cancer (0, 1.1%), and duodenal ulcer (0, 3.3%) [16]. This study demonstrated that upper GI endoscopy has a low diagnostic yield in PPI refractory patients.

Reflux Monitoring

Patients with PPI refractory reflux symptoms and normal endoscopy (NERD) should undergo further investigations, including 24 h pH monitoring and impedance testing. Patients with extraesophageal syndromes after exclusion of non-GERD-related etiology for their symptoms should be considered for reflux monitoring.

Currently, available tests for reflux monitoring are (1) catheter pH monitoring, (2) wireless pH, (3) combined multichannel pH monitor, and (4) esophageal Bilitec monitoring. Each technique has its limitations. Twenty-four hour pH monitoring has a sensitivity of 70–80% in typical GERD syndromes and the false negative rate ranges from 20 to 50%. With extraesophageal syndromes, the sensitivity is lower than with esophageal syndromes (50%). Day-to-day variation in acid exposure is an important reason for the high false negative rate. By extending pH monitoring to 48

or 96 h, a wireless ambulatory pH capsule can improve the diagnostic yield. In PPI refractory patients with negative catheter-based pH studies, our experience with Bravo is that it led to an increased diagnostic yield of 30% [17].

Charbel found that 31% of patients with typical symptoms and 30% of those with extraesophageal symptoms have abnormal pH testing (catheter based) [18] when treated with once-daily PPI, while with twice-daily PPI only 7% and 1%, respectively, had an abnormal pH test. The results suggested that once-daily PPI is insufficient to inhibit acid, and by increasing the dose, acidic reflux is no longer the main cause of patient's symptoms. Rather, non-acid reflux (NAR) is the main driver for patient's symptoms. Impedance pH study is the technique for detection of non-acid reflux, which can be liquid, gas, or mixture of both.

When a decision is made for reflux monitoring, two key issues need to be resolved: (1) what technique to use and (2) whether PPI therapy should be stopped for reflux monitoring. The technique chosen depends on the patient's clinical presentation (esophageal or extraesophageal) as well as the available technology and expertise. Reflux monitoring "off PPI" as well as "on PPI" offers clinically useful information, although there is no general agreement on which test has a higher diagnostic yield.

Reflux monitoring "off PPI" (7 days after cessation of PPI) can be performed using any of the available techniques described above. A negative test (normal esophageal acid exposure and negative symptom-reflux association) means that the patient is most likely to be suffering from functional heartburn [19]. Rome III definition of functional heartburn reflux refers only to 24 h pH monitoring, but the added value of impedance has to be considered, as non-acid reflux can be detected and therefore would reduce the proportion of functional heartburn (29% vs. 39% with 24 h pH only).

Reflux monitoring "on PPI" should be performed with impedance pH monitoring to allow detection of non-acid reflux [19]. The diagnostic yield with techniques other than impedance is very low, as in most acid-suppressed patients reflux is mainly non-acidic or usually acidic. It is not known whether wireless pH monitoring allowing both "off" and "on" PPI assessments could be more useful. Several reports have been published on the diagnosis made with PPI refractory patients tested with pH impedance: 50–60% of patients are non-GERD, 30–40% are caused by non-acid reflux, and 10% are due to acid reflux [20, 21]. Although uncommon, a positive test for acid reflux is evidence of therapeutic failure of GERD.

Studies comparing the yield of "on" and "off" PPI reflux monitoring are limited. A technical review on this issue suggested that the decision may be made based on the patient's clinical presentation. In patients with extraesophageal symptoms and without concomitant typical GERD symptoms, pH monitoring off medication may be more useful, as it will exclude GERD. In patients who have typical symptoms and partial response to PPI, it may be better off having reflux monitoring performed with PPI, as it would be possible to detect ongoing reflux due to therapeutic failure or noncompliance. For patients suspected of functional heartburn, off-therapy monitoring is preferred.

Another controversial issue is clinical value of SI or SAP. Slaughter et al. have shown that SI and SAP values were largely determined by chance occurrences [22]. Nonetheless, despite the shortcomings, analyses of symptom-reflux association are still clinically helpful to improve diagnosis of GERD-related symptoms.

Bilitec esophageal monitoring does not appear to be a first choice for diagnosis evaluation in PPI refractory patients, as the diagnostic yield is low and availability is limited.

Treatment of Refractory GERD

Optimizing PPI Treatment

The first step in the management of refractory is to optimize PPI therapy by checking compliance and confirming correct dosing, especially the evening dose rather than at bedtime.

Treatment of Residual Acid Reflux

After establishing compliance and correct dosing, increasing PPI to twice-daily dose or switching to another PPI could result in systematic improvement in roughly 20% of patients. There is no evidence to support further increase of PPI in those who failed PPI twice daily.

Lifestyle Modifications

Although lifestyle modifications such as weight loss and elevation of the head of the bed form part of the therapy for GERD, their value in refractory GERD patients has yet to be demonstrated. Recently, training the diaphragm by means of breathing exercises has been shown to improve GERD as assessed by pH study, quality of life, and PPI usage. There is no study to date that has shown clinical improvement in GERD symptoms by excluding coffee, chocolate, syrup, or fatty or spicy food [19].

Treatment Targeted at Residual Acidic Reflux

Based on the observation that 75% of patients taking PPI twice daily exhibit nocturnal acid breakthrough, H2RAs have been added at bedtime for patients with refractory GERD. Nocturnal acid control has been shown to improve. But there is a paucity of clinical data to show symptom improvement. Furthermore, patients taking H2RAs develop tachyphylaxis, and therefore most practitioners who use H2RAs use it intermittently or on demand.

Transient lower esophageal sphincter relaxations (TLESRs) are the main mechanism of all types of reflux—acidic, weakly acidic, or non-acidic. Currently, the only medication that can decrease TLESRs is baclofen, a $GABA_B$ agonist. Two studies have shown that baclofen can improve reflux-related symptoms [23, 24]. Baclofen use has been limited by CNS adverse effects. Many patients report dizziness, drowsiness, nausea, and vomiting. Newer $GABA_B$ agonists such as arbaclofen placarbil and lesogaberan have better tolerability but reduced efficacy.

Treatment Used for Gastroesophageal Motility

Prokinetic therapy with metoclopramide in addition to PPI is another option for patients with refractory GERD. Metoclopramide has been shown to increase lower esophageal sphincter pressure and accelerate gastric emptying. Domperidone is a peripherally acting dopamine agonist that has been demonstrated to improve gastric emptying too, but there is a paucity of data supporting its use in GERD. Metoclopramide has CNS side effects and in <1% of patients causes tardive dyskinesia. Checking for QT prolongation before starting domperidone may be prudent, as there is a small risk of ventricular arrhythmia.

Mosapride, a $5HT_4$ receptor agonist and weak $5HT_4$ receptor antagonist, has been shown to reduce acid reflux in the esophagus by improving esophageal motility and gastric emptying. In a study investigating efficacy with mosapride as an add-on therapy with omeprazole in PPI-resistant NERD patients, reflux symptoms and gastric emptying were shown to improve in a subset of patients with delayed gastric emptying. Itopride, a dopamine 2 agonist, has been used in patients as an acid or with PPIs for laryngopharyngeal reflux. Compared to placebo it has a faster improvement rate, but not greater efficacy. Rikkunshito, a traditional Japanese medicine, has been used in combination with PPI in patients with refractory GERD [25].

Targeting the Acid Pocket

A new target for treatment of reflux, and possibly refractory GERD, is the acid pocket. In the presence of a hiatus hernia, the acid pocket was more frequently located within the hiatus above the diaphragm, leading to increased acid reflux. In a pilot study, an alginate-antacid formulation has been recently demonstrated to reduce the number of acid reflux episodes by displacing the acid pocket below the diaphragm in patients with symptomatic GERD and large hiatus hernia. Confirmatory studies with larger number of patients will be needed before the alginate-antacid becomes standard therapy.

Treatment of Esophageal Hypersensitivity

Most patients with GERD symptoms refractory to PPI have normal esophageal acid exposure and normal endoscopy. On pH testing, they could have positive or negative symptom-reflux association. The latter group fulfills the criteria of functional heartburn (Rome III criteria), while the former group has been labeled as hypersensitive esophagus. In both groups, visceral hypersensitivity has a role. Pain modulators such as tricyclic antidepressants (TCAs), trazodone, and selective serotonin reuptake inhibitors (SSRIs) have all been shown to improve esophageal pain in patients with non-cardiac chest pain. According to current understanding, these agonists confer their visceral analgesic effect by acting at the central nervous system and/or afferent levels. The doses used are small and do not alter moods. For patients who have refractory heartburn and do not have access to esophageal impedance pH testing, a trial of one of these medications is an alternative. Other compounds that may potentially exert an influence on visceral hypersensitivity include citalopram, A_2D1386, and tegaserod. Further evaluation of these drugs is needed.

Endoscopic Therapy

Although short-term results with endoscopic devices have been encouraging, long-term efficacy has been elusive. A recent report of LINX reflux system made of titanium beads shows efficacy up to 4 years with few side effects in a multicenter trial and has obtained FDA approval [26].

Surgical Treatment

Laparoscopic fundoplication is effective in controlling acid and non-acid reflux. A recent randomized controlled study demonstrated that in PPI-responsive patients, esomeprazole and anti-reflux surgery achieved comparable rates of remission at 5 years. However, there is controversy on the efficacy of anti-reflux surgery in patients who have normal endoscopy and normal/abnormal acid exposure. It is prudent at this time to limit anti-reflux surgery to patients who are refractory to PPI and who have abnormal acid exposure when tested "off PPI."

Management algorithm of patients with PPI refractory symptom is shown in Fig. 8.1.

Conclusion

The advent of acid-suppressive drugs, in particular proton pump inhibitors (PPI), has revolutionized the management of GERD, with the promise that GERD could soon be a disease of the past. However, although many patients respond to PPI, refractory GERD has emerged as the new clinical challenge. Most, if not all, of

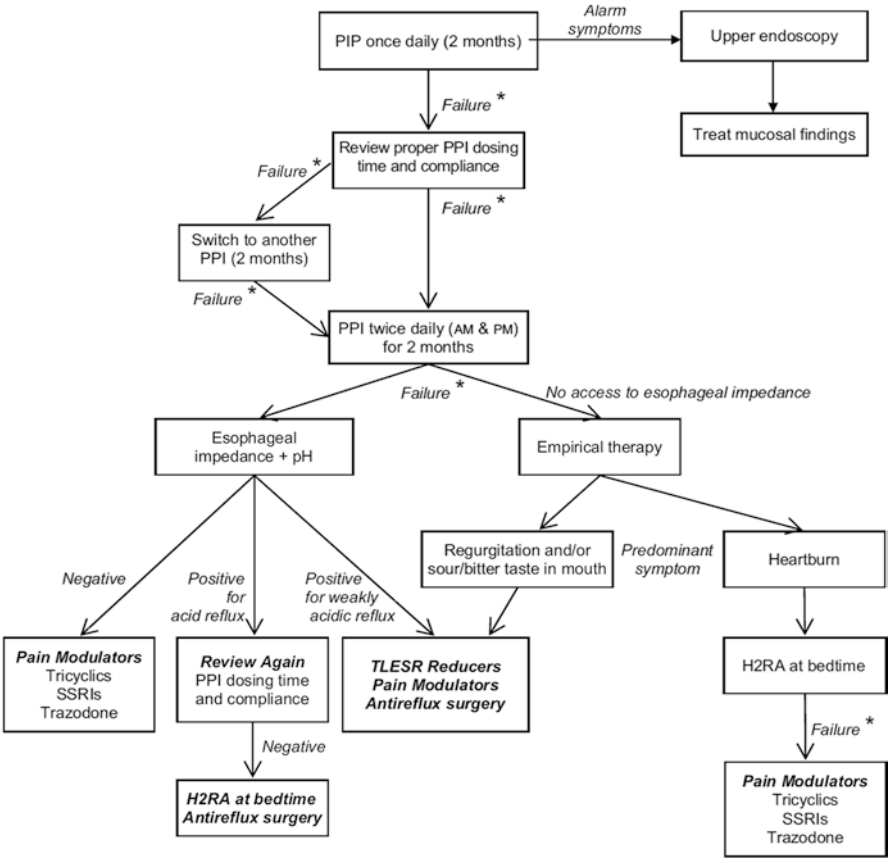

Fig. 8.1 Management algorithm of patients with PPI refractory symptom (Reprinted from Best Pract Res Clin Gastroenterol**,** Dec;24(6):923–36; Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD; © 2010, with permission from Elsevier)

these patients refractory to PPI are NERD and the extraesophageal syndromes. The reasons for their failure to respond to treatment are due to GERD-related or non-GERD-related etiologies. Currently, technologies to better measure pH and acid exposure in the esophagus have been developed to distinguish the PPI refractory GERD patients from non-GERD patients. It remains to be seen if the outcomes of treatment match the proposed mechanisms of PPI refractories.

References

1. Stifim D, Zebib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;61:1340–54.
2. Fass R, Ofman JJ. Gastroesophageal reflux disease – should we adopt a new conceptual framework? Am J Gastroenterol. 2002;97:1901–9.

3. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R. Global consensus group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–20. quiz 1943
4. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton pump inhibitor failure in gastro-esophageal reflux disease – what next? Aliment Pharmacol Ther. 2005;22:79–94.
5. Hershcovici T, Archem SR, Jha LK, Fass R. Systematic review: the treatment of non-cardiac chest pain aliment. Pharmacol Ther. 2012;35:5–14.
6. Kahrilas PJ, Howden CW, Hughes N, Molloy-Bland M. Response of chronic cough to acid suppressive therapy in patients with gastroesophageal reflux disease. Chest. 2013;143:605–12.
7. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA, et al. ACG clinical guidelines: evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013;108:379–92.
8. Savarino E, Pohl D, Zentilin P, Dulbecco P, Sanmito G, Sconfienza L, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. Gut. 2009;58(9):1185–91.
9. The Gallop Organisation. Gallop Study of Consumers' use of stomach relief products. Princeton: The Gallop Organisation; 2000.
10. Karamanolis G, Vanuystel T, Sifrim D, Bisschops R, Arts J, Caenepeel P, et al. Yield of 24-hour esophageal pH and Bilitec monitoring in patients with persisting symptoms on PPI therapy. Dig Dis Sci. 2008;53:2387–93.
11. Kahrilas PJ, McColl K, Fox M, O'Rourke L, Sifrim D, Smout AJ, et al. The acid pocket: a target for treatment in reflux disease? Am J Gastroenterol. 2013;108:1058–64.
12. Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan J. A comparison of the clinical demographic and psychiatric profiles among patients with erosive and non-erosive reflex disease in a multi-ethnic Asian country. World J Gastroenterol. 2009;11:3558–61.
13. Gerson LB, Kahrilas PJ, Fass R. Insights into gastroesophageal reflux disease – associated dyspeptic symptoms. Clin Gastroenterol Hepatol. 2007;5:690–5.
14. Fock KM, Teo EK, Ang TL, Tan JY, Lam NM. The utility of narrow based imaging in improving the endoscopic diagnosis of gastroesophageal reflux disease. Clin Gastroenterol Hepatol. 2009;7:54–9.
15. Miller SM, Goldstein JL, Gerson LB. Cost effectiveness model of endoscopic biopsy for eosinophilia esophagitis in patients with refractory GERD. Am J Gastroenterol. 2011;106:1439–45.
16. Poh CH, Gasiorowska A, Navaro-Rodriguez J, 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.
17. Ang D, Teo EK, Ang TL, Ong J, Poh CH, Tan J, et al. To Bravo or not? A comparison of wireless esophageal pH monitoring and conventional pH catheter to evaluate non-erosive gastroesophageal reflux disease in a multiracial Asian cohort. J Dig Dis. 2010;11:19–27.
18. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients as PPI therapy. Am J Gastroenterol. 2005;100:283–9.
19. Katz PO, Gerson LB, Vela MF. Guidelines for diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2001;108:308–28.
20. Mainie I, Tutuian R, Shays S, Vela M, Zhang X, Sifrim D, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicenter study using combined ambulatory impedance-pH monitoring. Gut. 2006;55:1398–402.
21. Zerbib F, Roman S, Ropert A, des Varannes SB, Pouderoux P, Chaput U, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. Am J Gastroenterol. 2006;101:1956–63.
22. Slaughter JC, Goutte M, Rymer JA, , Oranu AC, Schneider JA, Garrett CG, et al. Caution about over interpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2011;9:868–874.
23. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52:1397–402.

24. Cossentino MJ, Mann K, Armbruster SP, Lake JM, Maydonovitch C, Wong RK. Randomised clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux–a randomised prospective study. Aliment Pharmacol Ther. 2012;35:1036–44.
25. Tominaga K, Iwakiri R, Fujimoto K, Fujiwara Y, Tanaka M, Shimoyama Y, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. J Gastroenterol. 2012;47:284–92.
26. Ganz RA, Peters JH, Horgan S, Bemelman WA, Dunst CM, Edmundowicz SA, et al. Esophageal sphincter device for gastroesophageal reflux disease. N Engl J Med. 2013;368:719–27.