Digestive Diseases and Sciences (2018) 63:577–582
https://doi.org/10.1007/s10620-018-4927-5

REVIEW

Refractory Heartburn: A Challenging Problem in Clinical Practice

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Received: 3 July 2017 / Accepted: 10 January 2018 / Published online: 20 January 2018

Abstract
Gastroesophageal reflux disease (GERD) is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Heartburn and regurgitation are the typical symptoms of GERD. The treatment of GERD encompasses lifestyle modifications, pharmacological, endoscopic, and surgical therapy. The majority of the patients respond to 4–8 weeks of proton-pump inhibitors therapy, but 20–42% will demonstrate partial or complete lack of response to treatment. While these patients have been considered as having refractory heartburn, a subset of them does not have GERD or have not been adequately treated. The main causes of refractory heartburn include: poor compliance; inadequate proton-pump inhibitors dosage; incorrect diagnosis; comorbidities; genotypic differences; residual gastroesophageal reflux; eosinophilic esophagitis and others. Treatment is commonly directed toward the underlying cause of patients' refractory heartburn.

Keywords Gastroesophageal reflux · Drug therapy · Proton-pump inhibitors · Refractory GERD

Introduction

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications [1]. GERD prevalence is high, occurring in up to 20% of an urban population [1, 2]. While heartburn is the cardinal symptom of GERD, patients may experience a whole slew of symptoms including, regurgitation, chest pain, belching, water brash, and others.

GERD is associated with increased morbidity and a significant reduction in health-related quality of life. In addition, daily discomfort, repeated visits to a physician, the need of testing, and long-term treatment have all been associated with increased indirect and indirect cost in GERD [1].

There is no gold standard for diagnosing GERD, and consequently the diagnosis is sometimes not straightforward. This is compounded by the fact that upper endoscopy provides diagnosis when only esophageal erosions are documented, which occurs in only third of the cases.

Treatment of GERD has considerably improved with the introduction of proton-pump inhibitors (PPIs), which provide effective inhibition of gastric acid secretion. PPIs are usually prescribed in a standard dose and given in the morning 30 min before breakfast for a period of 8 weeks [2] in erosive esophagitis and 4 weeks in nonerosive disease (NERD). However, failure of PPI therapy may occur in 20–42% of the heartburn patients resulting in persistence of symptoms, the occurrence of new symptoms, and relapse of healed erosive esophagitis during maintenance therapy.

It has been proposed that refractory heartburn is defined as the persistence of typical heartburn that did not respond to a treatment with double dose PPI during a period of at least 8–12 weeks.

Refractory heartburn represents a heterogeneous group of patients with different underlying mechanisms for their symptoms, such as residual acid reflux, non-acid reflux, hypersensitivity to reflux, functional heartburn and other causes [3]. The term refractory GERD is not adequate in patients who are non-compliant, receive inadequate dose of PPI or those with non-GERD related or functional esophageal disorders.

This review summarizes and discusses the currently available information about refractory heartburn using PubMed, Medline, and other online sources. The following

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search terms were used: gastroesophageal reflux disease, acid reflux, heartburn, pyrosis, refractory GERD, and proton-pump inhibitors.

Mechanisms of Refractoriness

When treating a refractory heartburn patient, the physician first should consider whether the PPI dose is sufficient to control patient's symptoms. Improper PPI dosing is one of the causes of unsuccessful treatment.

It should be noted that patients with refractory heartburn more commonly display psychological comorbidities such as anxiety and depression as compared with patients who demonstrate an adequate PPI response [3]. On the other hand, one of the most important mechanisms that may contribute to persistence of heartburn symptoms is poor compliance or adherence to the prescribed PPI [4].

Patients with refractory heartburn encompasses three major subgroups:

(a) GERD patients with documented residual reflux [5].
(b) Functional heartburn or overlap between functional heartburn and GERD in patients with normal endoscopy, pH or pH-impedance testing and with no correlation between symptoms and gastroesophageal reflux events.
(c) Reflux hypersensitivity or overlap between reflux hypersensitivity and GERD in patients with normal endoscopy, pH or pH-impedance testing and with positive correlation between symptoms and gastroesophageal reflux events.

Identifying the aforementioned subgroups is very important because functional esophageal disorders prompt a different therapeutic approach as compared to the group with refractory GERD [6] (Table 1).

Table 1 Main causes of PPI failure in patients with heartburn

Reflux hypersensitivity
Functional heartburn
Poor compliance and adherence to PPI treatment
GERD misdiagnosis
Presence of comorbidities (psychologic, systemic disorders, etc.)
Genotype differences
Residual gastroesophageal reflux
Eosinophilic esophagitis
Skin diseases

Diagnosis

The workup of refractory heartburn includes the combination of endoscopy and esophageal function testing in order to categorize patients as having residual reflux, reflux hypersensitivity or functional heartburn. In this context, these diagnostic techniques are of utmost importance as they provide guidance to proper therapy (Fig. 1).

Upper Endoscopy

The usefulness of performing an upper endoscopy in young adult patients (< 40 years of age) with typical heartburn but without alarm symptoms has been questioned, resulting in empiric PPI treatment as the initial management in the majority of this patient population [2]. However, upper endoscopy can establish the diagnosis of erosive esophagitis, Barrett´s esophagus, and eosinophilic esophagitis in refractory heartburn patients. In addition, other esophageal mucosal abnormalities as well as gastric mucosal disorders, such as peptic ulcer can be excluded. Thus, the first diagnostic test that should be performed in patients with refractory heartburn is an upper endoscopy, which establishes the GERD phenotypic presentation of the patient when done off treatment and excludes other esophageal disorders [5].

Reflux Testing

The esophageal 24-hour pH test or the multichannel intraluminal impedance-pH test, which is not available in many countries, is the next test of choice for patients with refractory heartburn. In general, the catheter-based pH test or the wireless pH system should be used off PPI treatment in patients with no history of documented GERD on either previous upper endoscopy or pH test. If available, it is preferable to use the wireless pH capsule because it provides 48–96 h pH monitoring [7]. In those with documented history of GERD on previous upper endoscopy or pH test, pH-impedance should be used while patient is on PPI treatment.

Other Diagnostic Methods

High-resolution esophageal manometry (HREM) is the currently accepted method for the diagnosis of esophageal motor disorders and is useful to exclude major esophageal motor disorders in patients with refractory heartburn who demonstrated a negative upper endoscopy and normal pH or pH-impedance test. These include achalasia, esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, and absent contractility [6]. HREM can also exclude rumination and supra-gastric

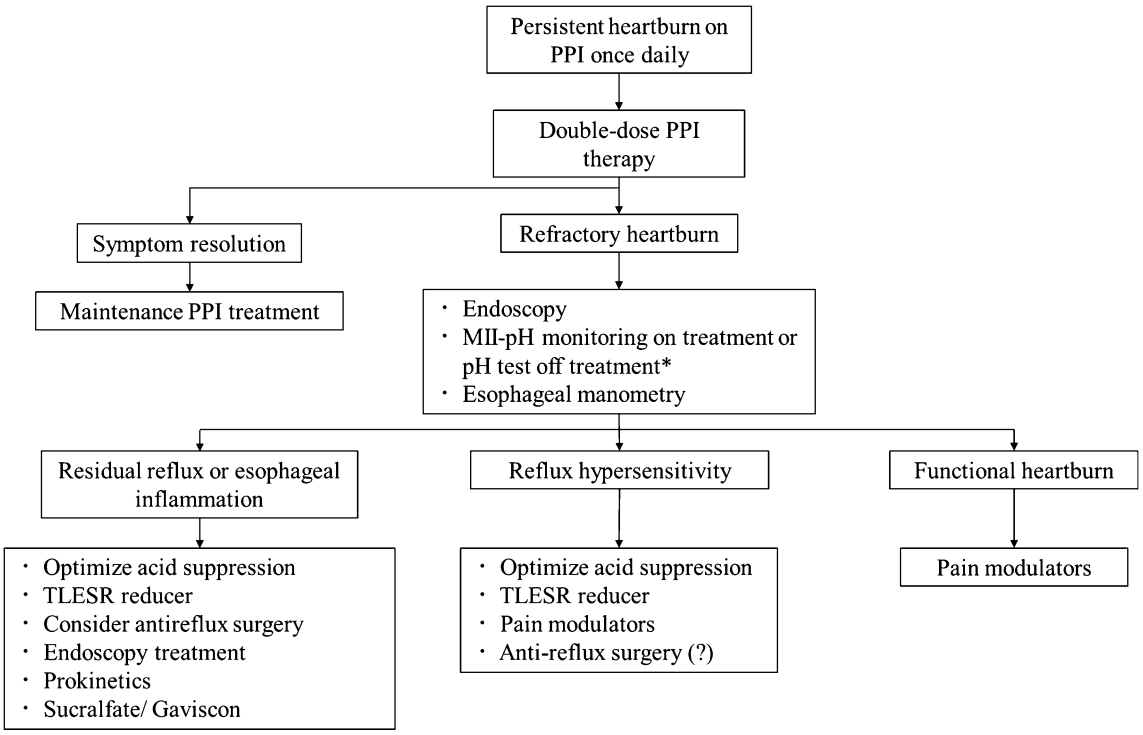

Fig. 1 Treatment algorithm of patients with refractory heartburn. *PPI* proton-pump inhibitor, *MII-pH* multichannel intraluminal impedance-pH, *TLESR* transient lower esophageal sphincter relaxation *In patients with history of documented GERD (positive upper endoscopy or pH testing), MII-pH should be performed on treatment. In those with no history of documented GERD, pH test off treatment (preferably wireless pH capsule) should be carried out. Adapted from Gyawali CP, et al. Gastroenterology. 2017. Epub ahead of print

belching which are not uncommonly confused with GERD [8]. Gastric scintigraphy in relevant patients can identify those with delayed gastric emptying.

Treatment

Functional Heartburn

Functional heartburn is a functional esophageal disorder with symptoms that mimic GERD. As defined by Rome IV [6], the diagnosis of functional heartburn is made after careful history and by identifying that burning retrosternal discomfort is the dominant symptom. In addition, diagnosis requires a stepwise evaluation that supports the absence of GERD, eosinophilic esophagitis, and a major esophageal motor disorder. The pathophysiology of symptom generation in functional heartburn is complex and not completely understood. However, the main mechanism appears to be altered esophageal pain perception due to esophageal hypersensitivity [10]. Development of esophageal hypersensitivity involves peripheral and central factors as well as psychoneuroimmunological interactions [6].

It is important to note that more than two-thirds of the patients referred with refractory heartburn do not have GERD [8]. Instead, these patients have other disorders, predominantly functional heartburn, and reflux hypersensitivity which require different therapeutic approaches.

Functional heartburn is treated with neuromodulators such as tricyclic antidepressants and selective serotonin reuptake inhibitors in low doses [10]. Psychotherapy, acupuncture, and hypnosis may also be beneficial, although there are very few studies to support their role in functional heartburn [11].

Poor Compliance and Adherence

Studies have demonstrated that up to 50% of patients with heartburn are non-compliant with PPI daily [12]. Because GERD is a symptom driven disease, compliance may depend on the presence of symptoms. Poor adherence to proper time of PPI administration has been also commonly observed in GERD patients, primarily because of lack of detailed instructions by the prescribing physicians [4].

PPIs only bind and irreversibly inhibit active proton pumps. Consequently, they are given before a meal to ensure their presence in the parietal cell canaliculi when proton pumps are activated. Giving PPIs with a meal significantly reduces their absorption and consequently their bioavailability. In addition, providing PPIs after a meal has been shown

to diminish their effect on intra-gastric pH [13]. However, in the USA, for example, about 70% of primary care physicians and 20% of gastroenterologists advise patients to take PPIs before bedtime and do not believe that taking PPI in relation to food is important [14].

When symptoms persist despite adequate compliance and adherence to treatment, the administration of double dose PPI should be considered. Up to 25% of patients report having satisfactory clinical response to twice daily PPI, given before breakfast and before dinner [15].

Comorbidities

In general, the frequency of other comorbidities in GERD patients increases with age. In one study, 87% of the patients with a mean age of 55 years had at least one comorbidity [16]. The common ones included, hypertension, dyslipidemia, obesity, depression, diabetes, and arthritis. GERD can be exacerbated and esophageal sensitivity can be altered in some of these disorders. In addition, the drugs used for the treatment of these disorders may also affect therapeutic response to PPIs. (Table 2).

Genotypic Differences

PPIs are metabolized in the liver by cytochrome P450 2C19 (CYP2C19). Although genotypic differences between patients are relatively uncommon, genetic variations may occur regarding the capability of an individual patient to metabolize PPIs. Thus, individuals who are "rapid metabolizers" of PPIs (CYP2C19*17 polymorfism) show a lower reduction in intra-gastric acidity and therefore lower rates of healing of erosive esophagitis [17]. In contrast, "slow" or "intermediate metabolizers" of PPIs demonstrate a longer half-life of the active metabolite of the PPI and thus improvement in the rate of erosive esophagitis healing. A recent meta-analysis demonstrated that CYP2C19 rapid metabolizers with erosive esophagitis have an increased risk of being refractory to PPI therapy as compared with poor metabolizers, suggesting that individualized PPI dosing regimen based on CYP2C19 genotype might be a valid therapeutic strategy for overcoming insufficient inhibition of gastric acid secretion [17]. However, this approach could be expensive and not readily available.

Table 2 Examples of drugs used for various comorbidities in GERD patients and their main adverse events in the upper gastrointestinal tract

Drug/indication	Adverse event
Statins/hypercholesterolemia	Dyspepsia, abdominal pain, nausea
Enalapril/arterial hypertension	Nausea, abdominal pain, dyspepsia, cough
Sibutramine/obesity	Nausea, vomiting
Fluoxetine/depression	Nausea, vomiting, dry mouth
Metformin/diabetes mellitus	Abdominal discomfort, nausea, vomiting
Nonsteroidal anti-inflammatory drugs/pain disorders	Epigastralgia, nausea, vomiting, dyspepsia, G.I. hemorrhage, peptic ulcer

Weakly Acidic Reflux

Esophageal pH-impedance provides assessment of the type of reflux that entered the esophagus. The test can identify non-acid reflux which constitutes weakly acidic reflux ($4 < pH < 7$), neutral reflux ($pH = 7$), and weakly alkaline reflux ($pH > 7$). Studies have demonstrated that 35% of the patients who failed PPI twice daily have non-acid reflux which may contribute to symptoms persistence [18]. Proximal migration of weakly acidic reflux and the presence of mixed liquid–gas reflux have been shown to increase reflux perception and thus symptom generation [19]. However, a major paradigm shift that has recently gained acceptance with the widespread use of pH-impedance testing is the understanding that esophageal hypersensitivity is an important underlying mechanism for refractory disease, especially in those with weakly acidic reflux [9]. Furthermore, it appears that many of these patients have in fact reflux hypersensitivity.

The management of patients with abnormal degree of weakly acidic reflux remains a challenge, because there is still no effective treatment for non-acidic reflux. In addition, outcome studies in patients with non-acidic reflux are also still lacking. However, in a recent study, the pH-impedance testing was utilized to tailor therapy in a group of patients with refractory heartburn. The authors concluded that two-thirds of the patients had their persistent reflux symptoms resolved with tailored therapy [20].

In patients with residual reflux (acidic or non-acidic), endoscopic treatment such as transoral incisionless fundoplication (TIF), and the Stretta procedure could be considered. However, their long-term value in non-acidic reflux has been scarcely studied. The same applies to the role of surgical fundoplication or sphincter augmentation in this patient population.

Treatment of patients with residual reflux (non-acidic) has been also directed toward transient lower esophageal sphincter relaxation rate with medications like baclofen [21]. However, the adverse event profile of the drug, including dizziness and sleepiness limited its use in clinical practice. Development of other $GABA_B$ receptor agonist, such as lesogaberan [22] and arbaclofen [23], was discontinued because of limited clinical efficacy and poor tolerance [5].

Autoimmune Skin Disorders

Some autoimmune skin disorders may affect the esophagus such as epidermolysis bullosa, pemphigus vulgaris, cicatricial pemphigoid, and lichen planus. Patients are usually middle-aged women who complain of heartburn and dysphagia. The skin lesions are not always characteristic of the disease. When esophagitis includes vesicles or blisters, mucosal biopsies should be obtained for direct and indirect immunofluorescence [24]. Treatment should be instituted by a dermatologist as it is necessary to have an experience with immunosuppression that these cases may require.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a disorder characterized by several esophageal symptoms that may be similar to those of GERD, such as heartburn, chest pain, and dysphagia. These occur in association with increase in esophageal eosinophilia, which is not responsive to acid suppression. Studies suggest that eosinophilia is common in esophageal biopsies from patients with GERD [25]. However, the prevalence of eosinophilic esophagitis is relatively low in patients with refractory heartburn and/or regurgitation symptoms on PPI treatment [25].

Conclusions

Patients who meet the criteria for refractory heartburn should first undergo upper endoscopy in order to exclude anatomical abnormalities in the esophagus and stomach.

Poor compliance and non-adherence to treatment, misdiagnosis, autoimmune skin disorders or eosinophilic esophagitis should be excluded. The presence of rapid metabolizers should also be considered.

When endoscopic findings are unrevealing, further investigation should be done based on availability of other diagnostic tools. The 24-hour pH test or the wireless pH capsule should assess refractory heartburn patients off treatment in those without documented history of GERD. In contrast, pH-impedance testing should be performed in refractory heartburn patients while on treatment in those with documented history of GERD.

In patients with residual reflux (acidic or non-acidic) in the context of refractory GERD or reflux hypersensitivity, TLESR reducers, endoscopic treatment, surgical fundoplication, and neuromodulators are possible therapeutic options.

Compliance with ethical standards

Conflict of interest Ronnie Fass was an advisor to Ironwood, Mederi Therapeutics, Allergan, Ethicon, Horizon, speaker for AstraZeneca, Takeda, Mederi Therapeutics and Horizon, and performed research for Ironwood and Salix. The authors Gerson Domingues and Joaquim Prado P. Moraes-Filho declare no conflict of interest.

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