

Gastroesophageal reflux symptoms not responding to proton pump inhibitor: GERD, NERD, NARD, esophageal hypersensitivity or dyspepsia?

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Gastroesophageal reflux (GER) is a common gastrointestinal process that can generate symptoms of heartburn and chest pain. Proton pump inhibitors (PPIs) are the gold standard for the treatment of GER; however, a substantial group of GER patients fail to respond to PPIs. In the past, it was believed that acid reflux into the esophagus causes all, or at least the majority, of symptoms attributed to GER, with both erosive esophagitis and nonerosive outcomes. However, with modern testing techniques it has been shown that, in addition to acid reflux, the reflux of nonacid gastric and duodenal contents into the esophagus may also induce GER symptoms. It remains unknown how weakly acidic or alkaline refluxate with a pH similar to a normal diet induces GER symptoms. Esophageal hypersensitivity or functional dyspepsia with superimposed heartburn may be other mechanisms of symptom generation, often completely unrelated to GER. Detailed studies investigating the pathophysiology of esophageal hypersensitivity are not conclusive, and definitions of the various disease states may overlap and are often confusing. The authors aim to clarify the pathophysiology, definition, diagnostic techniques and medical treatment of patients with heartburn symptoms who fail PPI therapy.

Key Words: *Gastroesophageal reflux disease; Heartburn; Proton pump inhibitor*

Symptoms suggestive of gastroesophageal reflux (GER; eg, heartburn, reflux or chest pain) affect up to 30% of the population in Western countries and their prevalence continues to increase (1-3). Management of patients with GER symptoms is one of the most expensive among chronic gastrointestinal disorders, with direct and indirect costs in the United States estimated to be \$10 billion annually (4). Proton pump inhibitors (PPIs) are the gold standard treatment for GER and account for two of the top-five selling drugs in the United States (5).

Recent studies have shown that approximately 10% to 40% of patients with GER symptoms fail to respond to standard-dose PPIs. Although PPI factors may play a role (such as inadequate dosing or nonadherence to treatment), other factors such as visceral hypersensitivity, upper gut dysmotility or inflammatory disorders, may underlie PPI failure (6,7). Based on a recent study (8), up to 35% of patients with PPI failure had an underlying pathology other than acid reflux.

Considering the economic burden of GER and PPI use on one hand and the substantial PPI failure rate on the other, it must be questioned whether acid suppression with PPIs is always being

Les symptômes de reflux gastro-œsophagien ne répondant pas aux inhibiteurs de la pompe à protons : RGO, RNE, RNA, hypersensibilité œsophagienne ou dyspepsie?

Le reflux gastro-œsophagien (RGO) est un processus gastro-intestinal fréquent qui peut provoquer des symptômes de brûlures d'estomac et de douleurs thoraciques. Les inhibiteurs de la pompe à protons (IPP) représentent la norme du traitement du RGO, mais un groupe important de patients qui en sont atteints n'y répondent pas. Par le passé, on pensait que le reflux acide dans l'œsophage était responsable de la totalité, ou du moins de la majorité, des symptômes attribués au RGO, y compris une œsophagite érosive et des manifestations non érosives. Cependant, les techniques d'examen modernes démontrent qu'en plus du reflux acide, le reflux de contenu gastrique et duodénal non gastrique dans l'œsophage peut également produire des symptômes de RGO. On ne sait pas si le liquide de reflux peu acide ou alcalin, au pH similaire à celui d'une alimentation normale, produit des symptômes de RGO. L'hypersensibilité œsophagienne ou la dyspepsie fonctionnelle accompagnée de brûlures d'estomac peuvent constituer d'autres mécanismes de production des symptômes, qui n'ont souvent rien à voir avec le RGO. Des études détaillées portant sur la physiopathologie de l'hypersensibilité œsophagienne ne sont pas concluantes, et les définitions des divers états de la maladie peuvent se chevaucher et prêter souvent à confusion. Les auteurs cherchent à présenter clairement la physiopathologie, la définition, les techniques diagnostiques et les traitements médicaux des patients ayant des symptômes de brûlures d'estomac qui ne répondent pas aux IPP.

used optimally for the treatment of GER symptoms. Thus, a better understanding of the underlying etiologies of these symptoms may help to optimize treatment. In the present review, we discuss the potential mechanisms involved in the genesis of symptoms in patients with GER, possible causes of PPI failure, diagnostic tests and available treatments for PPI failure.

DEFINITION AND ETIOLOGIES OF GER SYMPTOMS

Gastroesophageal reflux disease, nonerosive reflux disease, nonacid reflux disease, functional esophageal disorders and noncardiac chest pain

GER symptoms include the classic definition of reflux – a rising retrosternal burning sensation. In English, the terms 'reflux' and 'heartburn' are generally used interchangeably. Chest pain (typically after cardiac evaluation rules out cardiac sources and, thus, termed 'noncardiac chest pain' [NCCPI]) is also commonly included as a GER symptom but dysphagia is not. GER symptoms may result from acid reflux, esophageal hypersensitivity, sustained esophageal contractions or

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abnormal tissue resistance (9). The nomenclature for etiologies of GER symptoms can be confusing and the definitions may overlap.

GER disease (GERD) is caused by the reflux of gastric contents into the esophagus and may or may not induce esophageal injury, although the original definition (in the pre-PPI era) usually meant erosive esophagitis (10,11). The mechanisms underlying GERD remain debatable (12); however, transient lower esophageal sphincter relaxation (TLESR), hypotensive lower esophageal sphincter (LES) and retrograde movement of gastric or duodenal contents into the esophagus are the accepted major pathologies in GERD (13).

Nonerosive reflux disease (NERD) refers to the presence of GER symptoms attributed to the (typically acidic) reflux of gastric contents into the esophagus but without endoscopically visible esophageal inflammation.

Esophageal hypersensitivity may be an independent phenomenon or may overlap with GERD. It describes a condition in which an esophageal stimulus that does not lead to any esophageal injury induces symptoms such as heartburn and chest pain. In other words, patients with esophageal hypersensitivity have a lower threshold for the perception of physiologically nonpainful stimuli (14). According to the American Gastroenterological Association consensus on GERD (15), hypersensitivity symptoms are attributable to reflux events, whereas functional heartburn is not associated with reflux events. Despite this definition, esophageal hypersensitivity may be apparent in GERD, nonacid reflux disease or weakly acid reflux disease, and functional esophageal disorders.

Esophageal hypersensitivity has overlap with functional esophageal disorders including functional heartburn, functional chest pain of presumed esophageal origin or NCCP. Functional heartburn is a controversial issue from both the diagnostic and pathophysiological perspectives. According to the Rome III criteria, burning retrosternal discomfort or pain without any evidence of gastroesophageal acid reflux or esophageal motility disorder for the past three months and with symptom onset at least six months before the diagnosis is defined as functional heartburn. The symptoms of these patients are often indistinguishable from GERD. The Rome committee suggested that histopathology and a gastroesophageal acid reflux work-up should be performed to rule out acid reflux and eosinophilic esophagitis in these patients (16,17). Based on the Rome III criteria, chest pain without evidence of GERD or esophageal motility disorder is known as functional chest pain of presumed esophageal origin. Acidity, mechanical distension, osmolality, temperature, as well as esophageal muscular contractions have been considered to be potential causes of the chest pain in this group. Finally, NCCP is defined as angina-like chest pain in patients in whom a cardiac pathology is ruled out (18,19).

Esophageal motility disorders and eosinophilic esophagitis

Esophageal motility disorders, such as diffuse esophageal spasm, may also present with GER symptoms (eg, reflux and chest pain), but patients rarely complain about reflux as the sole symptom (20). Eosinophilic esophagitis is an increasingly common cause of GER symptoms and dysphagia. Because esophageal intramucosal eosinophilia is a frequent finding associated with GERD, lack of histological response to high-dose PPIs should be considered before making the final diagnosis (21-23). On the other hand, in recent years, a form of esophageal eosinophilia has been recognized that responds to PPI therapy. The recognition of PPI-responsive esophageal eosinophilia (PPI-REE) has made the diagnosis of eosinophilic esophagitis more difficult because lack of response to PPI therapy was a previously important diagnostic criterion for eosinophilic esophagitis. As a result, based on recent guidelines, exclusion of PPI-REE with a PPI is required for the diagnosis of eosinophilic esophagitis. Whether PPI-REE is a form of GERD-induced esophageal eosinophilia is not clear. To determine whether reflux is the underlying cause of eosinophilia, further evaluation for NERD may be necessary (24,25).

GERD not only presents with esophageal symptoms but also may manifest with symptoms of dyspepsia (26). Therefore, it is wise to

test for acid reflux in dyspeptic patients with dominant esophageal symptoms.

In summary, symptoms of GER (eg, heartburn or chest pain) may occur with acid reflux, nonacidic or weakly acidic reflux, functional esophageal disorders, esophageal motility disorders, eosinophilic esophagitis or other organic/anatomical disorders of the esophagus. All of these etiologies should be considered in patients with GER symptoms. Moreover, drugs, such as nonsteroidal anti-inflammatory drugs, tetracyclines and bisphosphonates, may induce esophagitis and GER symptoms (27).

CURRENT APPROACH TO PATIENTS WITH GER SYMPTOMS

Taking an appropriate history is an important step in diagnosis. Accompanying symptoms and a drug history are two important parameters that must be included. Review of eating habits and diet may be helpful in some patients (ie, avoiding large meals just before bed or raising the head of the bed); however, there is little evidence to support these interventions. Weight loss may appreciably improve GER symptoms (28). Urgent upper endoscopy is required for evaluation of patients with alarm symptoms (dysphagia, vomiting, weight loss, anemia or an abnormal physical examination). In patients with GER symptoms and no alarm features, acid suppression therapy using a regular dose of PPI for at least eight weeks should be started (Table 1).

DIAGNOSTIC APPROACH TO REFRACTORY PATIENTS

Initial response to PPI therapy should be assessed clinically after four to eight weeks. Failure to respond to a regular dose of PPI is defined as refractory GERD (6,15). In patients with persistent symptoms, assessment of the method of administration of PPI is important because patients frequently perform it incorrectly. Doubling the dose of PPI or switching to another PPI may also be beneficial, although the evidence for these manoeuvres is weak. In refractory patients or those with new or worsening symptoms on high-dose PPIs, endoscopy and biopsy are indicated (10). The current approach to PPI failure is summarized in Figure 1. Although the majority of patients with GERD are adherent to PPI therapy (29), PPI failure may occur in patients who take PPIs incorrectly. Failing to take doses 30 min to 60 min before a meal will lead to lower effectiveness because gastric acid production is stimulated by food, and the proton pumps are inactivated by PPI during acid production. A common example is taking PPI at bedtime for night-time symptoms, which is less effective than taking the dose before the evening meal. This is a more important issue for an immediate-release PPIs but less so for a PPI with a dual-dose (combined immediate release/slow-release) formulation such as dexlansoprazole. Similarly, failing to take the medication at all or infrequent, as-needed use will significantly reduce the overall benefit from PPI.

Variability in PPI metabolism is another possible cause of PPI failure that is less well understood. Cytochrome P450 is the major enzyme involved in the metabolic degradation of PPIs, with CYP2C19 and CYP3A4 isoenzymes being the most important (30). Patients with the CYP2C19 wild-type allele are considered to be rapid metabolizers and those who possess the CYP2C19*17 allele are ultrarapid metabolizers. Rapid metabolizers will have lower serum levels of PPI, leading to less effect. The clinical benefit of CYP2C19 genotype testing in GERD, and especially in PPI failure, is unclear (31), particularly because it is easier to empirically increase the dose than to perform genotypic analysis. The potential causes of PPI failure are summarized in Table 2.

Insufficient response to high-dose PPIs in patients with normal endoscopy and biopsy is an indication for esophageal manometry and esophageal pH monitoring (6,15). Manometry is generally required to document the location of the lower esophageal sphincter for suitable pH probe placement. In certain cases, significant primary esophageal motility disorders that may lead to symptoms of reflux or regurgitation (such as achalasia or scleroderma) may also be diagnosed on manometry.

TABLE 1
Potential medications for gastroesophageal reflux symptoms

Class	Mechanism	Medication	Standard dose	Double-dose (refractory)
Proton pump inhibitors	Inhibition of gastric acid secretion through blocking (H ⁺ , K ⁺)-ATPase enzyme	Omeprazole	20 mg daily	20 mg twice daily
		Pantoprazole	40 mg daily	40 mg twice daily
		Esomeprazole	40 mg daily	40mg twice daily
		Rabeprazole	20 mg daily	20 mg twice daily
		Lansoprazole	30 mg daily	30 mg twice daily
Prokinetics/TLESR inhibitors	D2 receptor antagonist Peripherally acting D2 receptor antagonist Gamma-aminobutyric acid-B receptor agonists	Metoclopramide	10–15 mg up to 4 times daily	
		Domperidone*	10 mg 3 times daily	
		Baclofen	10–20 mg 2–3 times daily	
Antinociceptives	Tricyclic antidepressants	Imipramine	10–50 mg at bedtime	
		Nortriptyline	10–25 mg at bedtime	
		Trazodone	100–150 mg at bedtime	
	Serotonin reuptake inhibitors	Sertraline	50–200 mg at bedtime	
		Paroxetine	10–40 mg daily	
	Serotonin and norepinephrine reuptake inhibitors	Venlafaxine	75 mg daily	
Inhibiting excitatory neurotransmitter release	Pregabalin	50 mg 3 times daily		

Data adapted from references 60, 85-87. *In patients with dyspepsia and delayed gastric emptying. TLESR Transient lower esophageal sphincter relaxation

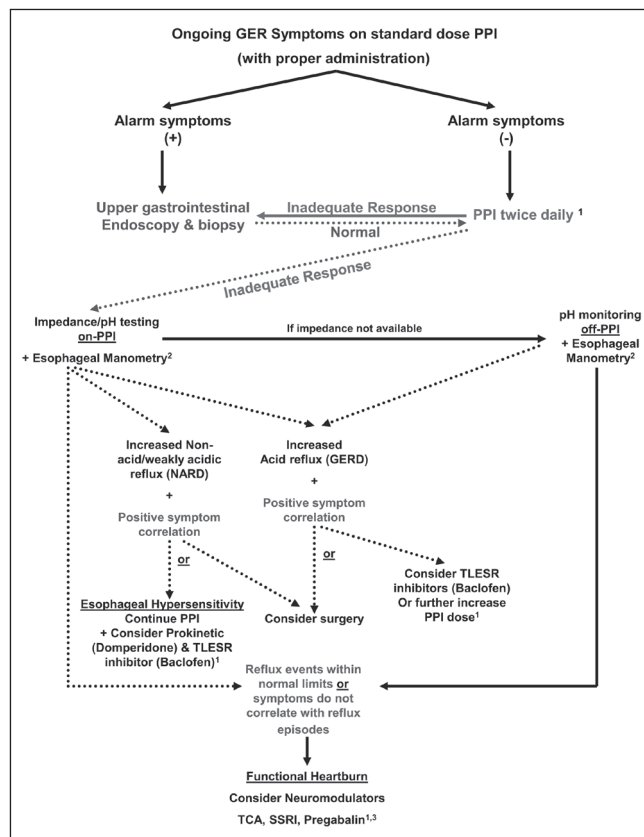


Figure 1 Approach to proton pump inhibitor (PPI) failure in patients with gastroesophageal reflux (GER) symptoms. Alarm symptoms: weight loss, dysphagia, gastrointestinal bleeding, age >55 years, etc. ¹If additional dyspeptic symptoms, treat as functional dyspepsia; ²If esophageal manometry shows specific diagnosis (eg, achalasia or spastic disorder), treat as appropriate, if only nonspecific, abnormalities are apparent (eg, ineffectual esophageal motility), continue on pathway; ³Consider transient lower esophageal sphincter relaxation (TLESR) inhibitors if the diagnosis is based on pH monitoring and not impedance testing. TCA Tricyclic antidepressant; SSRI Selective serotonin reuptake inhibitor

TABLE 2
Causes of proton pump inhibitor (PPI) failure

PPI related	Insufficient dose
	Nonadherence
	Genetical/pharmacological rapid/ultra-rapid metabolism
Reflux related	Nonacid/weakly acidic reflux
	Esophageal
Esophageal	Esophageal hypersensitivity
	Esophageal motility disorders
	Eosinophilic esophagitis
	Anatomical abnormality (eg, hiatal hernia, malignancy)
	Gastric
Gastric	Dyspepsia
	Gastroparesis

Esophageal pH testing

Esophageal pH testing has been used for decades to measure the degree of acid exposure in the esophagus. Transnasal catheter-based methods remain the most commonly used in Canada and are typically left in situ for 24 h. Wireless, capsule-based pH testing methods that are fixed to the esophageal mucosa (Bravo system, Given Imaging Inc, Israel) are also available and are typically measured over 48 h. Patients push a button on a pH recorder when they experience symptoms so that the symptom event may be correlated with the presence or absence of a reflux event. Acid reflux is defined as a pH <4 in the esophagus.

The sensitivity of pH testing for acid reflux is obviously optimal with patients off PPIs. Thus, a pH study used to document the severity and extent of acid reflux in the natural state (eg, for preoperative work-up for a fundoplication) should be performed with the patient off PPIs for five to seven days before the study. However, if a patient continues to experience symptoms on PPIs, performing a standard pH study with the patient on PPIs may only yield information about acid breakthrough and will not provide any information about nonacidic reflux events. A normal pH study on PPIs suggests either nonacid reflux or esophageal hypersensitivity, but will not be able to differentiate between the two (32).

Esophageal impedance testing

Esophageal multichannel intraluminal impedance (MII) testing is a catheter-based method similar to catheter-based pH testing. By recording changes in resistance to electrical currents, numerous impedance sensors on the catheter can measure both bolus type (liquid or gas)

and direction (aboral or oral), regardless of pH in the esophagus. The catheter also contains standard pH sensor(s) so that boluses can be characterized as acidic or otherwise. In patients with refractory symptoms, MII is recommended (6); however, consensus has not yet implemented this as a routine approach (10,15). Using this technique, it was discovered that nonacidic reflux from the stomach into the esophagus was common. Using combined pH/impedance testing, GER is generally grouped into classical acid reflux (pH <4) or nonacid reflux (pH >4). The latter can be categorized into weakly acid (4 <pH <7) and weakly alkaline reflux (pH ≥7) (33,34).

Based on a study using pH/II monitoring, the majority of symptomatic reflux episodes in patients who failed to respond to a PPI were weakly acidic (35). This study, along with others, suggests high proximal extent of the refluxate and sensitization of the esophagus by preceding acid exposure as the most probable causes of sustained symptoms in patients treated with a PPI (35-37). Another study revealed that impedance testing of patients with NERD for possible underlying nonacid reflux decreased the number of patients diagnosed with functional heartburn (38). Accordingly, we can speculate that patients who were diagnosed with functional heartburn in the preimpedance testing era should now be retested, and grouped into patients experiencing either nonacid reflux or nonreflux disorders. Because there may be a substantial overlap between functional heartburn and nonacid reflux, esophageal impedance testing may help in clarifying it to some extent (33).

In patients with inadequate response to PPI treatment, it is important to assess the relationship between patients' reported symptoms and esophageal acid or nonacid reflux events. For this, indexes, such as the symptom index and symptom association probability, are used. These indexes and their value and limitations are clearly discussed elsewhere (39).

Testing for esophageal hypersensitivity

Because esophageal hypersensitivity represents a lowered threshold of perception and symptoms in response to the same degree of chemical, mechanical, emotional or unidentified stimuli (14), lack of diagnostic methods and variability of the stimuli make the diagnosis of this condition challenging.

A convenient diagnostic test for esophageal hypersensitivity in the presence of acid reflux is not available. In the 1950s, Bernstein and Baker (40), and Bernstein et al (41) introduced a test for the diagnosis of esophagitis using mild hydrochloric acid infusion into the esophagus to induce esophageal pain in patients with GERD. A positive test result was defined as the generation of typical GERD symptoms. At that time, Bernstein and Baker could not perform esophageal pH monitoring to define a clear association between acid reflux and GERD symptoms. Subsequently, Jung et al (42) performed both esophageal pH monitoring and a Bernstein test simultaneously in patients with heartburn, and no correlation between positive symptom indexes and positive Bernstein results was apparent. Esophageal hypersensitivity to acid stimulation may be a distinct category that may not be related to acid reflux; the benefit of a Bernstein test within the diagnostic approach to GERD or functional esophageal disorders is undefined.

The potential role of esophageal hypersensitivity in nonacid reflux is not known. It is not clear what induces symptoms in patients with weakly acidic or alkaline reflux. A previous study showed that patients with GERD, and especially those with NERD, are hypersensitive to esophageal perfusion with acid as well as with saline (43). This finding also supports the non-acid-dependent role of esophageal hypersensitivity in the presentation of reflux symptoms (43). Interestingly, another study showed that infusion of bile salts into the esophagus can induce pain in 100% of patients previously diagnosed with functional heartburn and also induced pain in some of the healthy controls (44).

In a previous study, despite negative endoscopy and pH monitoring, approximately 30% of individuals who were chronically using antacids for heartburn experienced esophageal hypersensitivity to both acid and mechanical stimuli (45). Another study showed that patients with a

history of functional heartburn with negative pH monitoring and PPI failure were more sensitive to both esophageal balloon distention and acid perfusion compared with patients with NERD (46). It was also shown that patients with normal acid exposure but symptom-associated reflux events ≥50% had a lower threshold for both initial perception and discomfort in response to esophageal balloon distention compared with healthy controls or patients with acid reflux (47). Based on studies using a balloon-distension test, approximately 80% of patients with functional chest pain have a hypersensitive esophagus with lower thresholds for perception, discomfort and pain (48,49). Moreover, studies showed no symptoms after acid perfusion in up to 90% of patients with NCCP (50) and hypersensitivity to acid is not a general phenomenon in patients with functional heartburn because these patients have more somatization features, reports of chest pain and changes in autonomic function compared with NERD patients with abnormal pH recordings (51).

The above-mentioned studies indicate that esophageal exposure to high or low pH, as well as mechanical stimulation, may induce symptoms in patients with GERD and/or functional esophageal disorders. Regardless of the reflux contents, it should be emphasized that esophageal hypersensitivity may play a critical role in the development of heartburn. In patients with GER symptoms, visceral hypersensitivity may occur as a consequence of long-term exposure to acid or nonacid reflux, or may even be present without exposure to erosive substances. However, it remains unclear whether esophageal hypersensitivity is a primary or secondary phenomenon. The concept of hypersensitivity following a previous insult has been suggested to play a major role in other hypersensitivity disorders (eg, irritable bowel syndrome) in which a previous infection triggers visceral hypersensitivity (52). Exposure to acid may, thus, be the initial insult inducing esophageal hypersensitivity later in life. Whether and how weakly acidic or weakly alkaline reflux potentially induce hypersensitivity has yet to be studied. One previous study showed that experimental short exposure of rabbit esophageal mucosa to bile acids in acidic, weakly acidic or neutral conditions may change mucosal permeability and, in some conditions, may impair esophageal mucosal integrity (53). Other potential underlying mechanisms include activation of acid-sensitive ion channels or esophageal mechanoreceptors, changes in afferent sensory neuron conductivity, as well as alterations in central processing; all of these warrant further investigation (46,54). Dilatation of intercellular spaces has also been reported in patients with GERD (55,56).

Collectively, GER symptoms may be apparent in patients with acid reflux, nonacid reflux, esophageal hypersensitivity, esophageal dysmotility, eosinophilic esophagitis and other organic diseases. Therefore, in patients with GER symptoms and PPI failure, a comprehensive evaluation may often be required including endoscopy with biopsy, esophageal manometry and combined pH/impedance testing.

Tests in patients with refractory GERD with dyspepsia

Patients with dyspepsia present with epigastric pain or burning, early satiety and postprandial fullness. The differential diagnosis of dyspepsia is broad and because it has substantial overlap with GERD, a work-up is essential to differentiate GER symptoms with an underlying esophageal pathology from dyspeptic patients with additional GERD-suggesting symptoms. Studies have shown that 10% to 33% of patients with GERD have some form of delayed gastric emptying. It appears that delayed gastric emptying correlates with less acidic but more voluminous refluxate to the proximal esophagus (57,58). Most patients with refractory GERD do not require gastric emptying testing unless they also have symptoms of severe dyspepsia, vomiting or gastroparesis.

MEDICAL TREATMENT OF REFRACTORY GER SYMPTOMS

Current medications

As mentioned, GER symptoms may be caused by acid reflux, nonacid reflux, motility disorders of the esophagus, esophageal hypersensitivity,

eosinophilic esophagitis or other organic diseases. After ruling out alarm symptoms, treatment of patients with GER symptoms primarily consists of avoiding culprit foods and exacerbating behaviours, losing weight and acid suppression with a regular-dose PPI (Table 1).

In refractory GER symptoms and in the absence of alarm symptoms, patients are treated with double-dose PPI (6). In rapid metabolizers, giving even higher doses of PPI (quadruple dose) may be beneficial (31). Because genotype testing for metabolism alleles is generally not available, the rationale for giving more than double-dose PPI would have to be based on a pH study that shows persisting significant acid reflux despite correctly administered PPI use.

By including esophageal hypersensitivity as a possible cause of patients' symptoms, visceral analgesics can be beneficial in the treatment of patients with GER symptoms who do not respond to double-dose PPI treatment. Pain modulators, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) all improve esophageal pain in patients with NCCP and are helpful in patients with refractory GERD (59). Based on a systematic review of antidepressants in patients with NCCP, which included six randomized trials studying SSRIs (paroxetine and sertraline), tricyclic antidepressants (imipramine), SNRI (venlafaxine) and a triazolopyridine (trazodone), the percentage reduction in chest pain with venlafaxine, sertraline and imipramine was 50% to 63%, while it was 1% to 15% in the placebo group. This improvement was independent of improvement of depression scores. On the other hand, the adverse effects were relatively high in the treated groups and were the reported reason for discontinuation of trials in 53% of patients from the antidepressant groups (60). The effective doses of these antidepressants are summarized in Table 1.

Moreover, we know that TLESRs play a crucial role in the pathophysiology of GERD. Prokinetics, such as dopamine-2 receptor antagonists (eg, metoclopramide and domperidone), and TLESR inhibitors such as gamma-aminobutyric acid-B receptor agonists (eg, baclofen), are helpful in patients with refractory GERD. Although baclofen decreases the symptoms in some patients, the symptomatic benefit remains poor in others (61-63).

All potential medications, including antinociceptives and TLESR inhibitors, should be given in combination with PPIs because given alone, their effect on patients symptoms is poor (33).

Potential medications for the treatment of GERD symptoms are summarized in Table 1. In addition, a trial of antidyspeptic drugs including phytotherapeutics (such as STW5) could be considered.

Future treatments

Reflux inhibitors: Novel TLESR inhibitors, such as metabotropic glutamate receptor 5 antagonists (eg, AZD2066) are potential treatments for patients with refractory symptoms (64). Cannabinoid receptor agonists potentially inhibit TLESR; therefore, they may be potential treatment for patients with GER symptoms (65,66).

Antinociceptives: One possible future direction in the therapeutic area of esophageal hypersensitivity is the development of analgesic medications that specifically target receptors such as transient receptor potential cation channel subfamily V member 1 (TRPV1), a receptor that was shown to be crucially involved in the pain sensation pathways of the esophagus (54,67,68). To support this, a recent study has shown that a TRPV1 antagonist (AZD1386) increases esophageal pain thresholds in human (69). Targeting protease-activated receptors (eg, PAR-2), which are involved in both nociception and LES relaxation, or cholecystokinin with their antagonists would be potential treatments in patients with GER symptoms (36,70,71).

Mucosal protection with medications such as sucralfate (72) or those which affect esophageal bicarbonate/mucin secretion (73) are other possible treatments that should be considered in patients with refractory symptoms.

Cannabinoids with both central and peripheral antinociceptive effects are potential treatments for esophageal hypersensitivity (65).

Surgical and endoluminal therapies

Interventional strategies for the treatment of GERD are primarily based on mechanical blocking of the LES and, therefore, decreasing the episodes/amounts of gastric reflux into the esophagus. The real indications of interventional treatments of GERD are not well defined. Regurgitation, respiratory symptoms, acid reflux and nonacid/weakly acidic reflux both with positive symptom correlation are potential indications of interventional treatment of patients with GER symptoms; however, more studies are needed to define the actual therapeutic effect of these interventional methods (74-76).

PPI FAILURE DUE TO PPI SIDE EFFECTS

Studies have shown acid-related symptoms and rebound acid hypersecretion may occur after PPI treatment (77-79). Aside from rebound acid hypersecretion, rare side effects that have been associated with long-term PPI treatment include hypomagnesemia, abdominal symptoms (cramps, pain or diarrhea), *Clostridium difficile* infection, small intestinal bacterial overgrowth and spontaneous bacterial peritonitis (80-82). Moreover, PPIs may delay gastric emptying and cause dyspepsia in certain patients (83). In general, PPIs are safe and well-tolerated medications, but it is important to be aware of their rare side effects that may mimic PPI failure.

RECOMMENDATIONS AND CONCLUSIONS

Nonacid reflux and esophageal hypersensitivity are not sufficiently considered in the management of patients with heartburn or NCCP, especially when the patients fail to respond to a PPI treatment. The definitions of 'functional heartburn' and 'functional chest pain of presumed esophageal origin' need to be re-evaluated because heartburn or chest pain are clearly more than just a consequence of acid reflux.

A failure of PPI, after exclusion of organic (eg, eosinophilic esophagitis) or drug (eg, nonsteroidal anti-inflammatory drugs) -related reasons may occur under three major possible conditions: nonacid esophageal reflux; esophageal hypersensitivity; and CYP2C19 polymorphisms. Esophageal hypersensitivity occurs with or without reflux, independent of the pH of the refluxate.

Considering the potential overlap among esophageal hypersensitivity, acid and nonacid reflux, functional heartburn and dyspepsia, esophageal impedance testing is valuable in both the clinic and in research. In this regard, the importance of esophageal impedance testing is clear, especially in the management of patients with refractory symptoms; however, the role of provocative and sensory assessments needs to be further elucidated.

CONCLUSION

Patients with GERD, functional heartburn or NCCP may experience esophageal hypersensitivity to chemical, mechanical or other stimuli. Studying esophageal hypersensitivity in patients with GERD-indicating symptoms may change our understanding of GERD and other functional esophageal diseases. Therefore, one potential future direction in the diagnosis of patients with refractory heartburn or NCCP may be sensory assessment with multimodal probes integrating electrical, mechanical, thermal and chemical stimuli (84) in addition to esophageal impedance, pH and motility testing. Additionally, pharmacogenomics may help us in selecting sufficient doses of PPIs and predicting response to therapy.

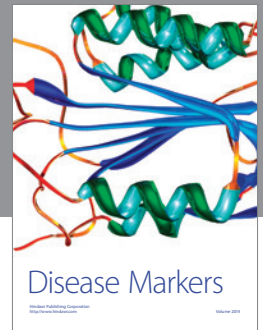
While response to PPIs in patients with GER symptoms is promising, antinociceptive medications and TLESR inhibitors are beneficial in refractory cases.

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