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Refractory GERD, beyond proton pump inhibitors

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Pharmacologic therapy, surgery, minimally invasive therapies, and alternative therapies are different options available for the management of refractory GERD. The choice may depend on the cause of refractoriness. Increased gastric acid suppression therapy might be useful in the rare patients with persistent elevated esophageal acid exposure on proton pump inhibitors (PPI). Potassium-competitive acid blockers (P-CAB) might induce a more important acid inhibition than PPI. Baclofen might act as a reflux inhibitor and demonstrates a significant efficacy in rumination syndrome. The role of topical antacid–alginate in refractory GERD might be limited. Surgery might be a valid option in case of persistent pathological acid esophageal exposure despite PPI. Further evaluation of minimally invasive procedures is necessary. Finally diet, diaphragmatic breathing and transcutaneous electrical acustimulation might be of interest in patients with esophageal hypersensivity or functional symptoms.

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The resistance to proton pump inhibitors (PPI) therapy is an increasing problem in patients with symptoms suggestive of gastro-esophageal reflux (GERD). In a systematic review El-Serag *et al.* estimated that around 30% of patients included in randomized trials and up to 60% of patients included in observational studies in primary care settings had GERD symptoms that did not respond to PPI therapy [1]. Different mechanisms might explain the persistence of symptoms: first, a persistent pathological esophageal acid exposure on PPI, second, an elevated number of weakly acidic reflux episodes on PPI, third, a reflux hypersensitivity (defined as a normal esophageal acid exposure, a normal number of reflux episodes but a positive association between reflux and symptoms), and fourth, functional symptoms without real GERD (normal esophageal acid exposure, normal number of reflux episodes, negative association between reflux and symptoms) [2]. The treatment of refractory symptoms should target the underlying mechanisms of symptom generation identified with complementary examinations (Figure 1).

This review is focused on the recent therapeutic options proposed for the management of refractory GERD. For each option, the potential indications are presented.

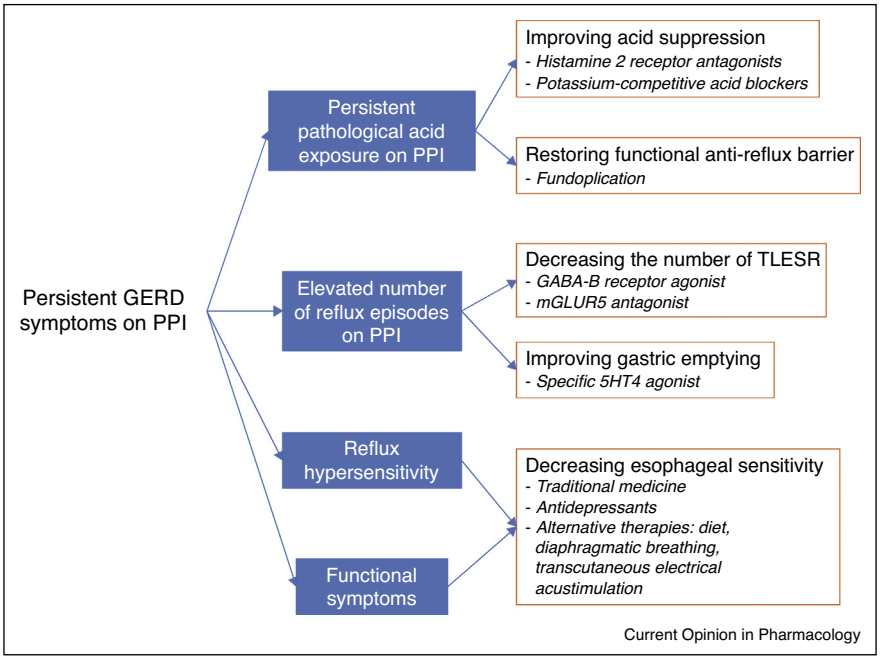
Pharmacological treatment

Improving acid suppression therapy

Increasing the level of gastric acid suppression may be of interest when esophageal acid exposure remains abnormal despite PPI therapy. A study conducted among expert esophagologists revealed that adjunction of histamine-2 receptor antagonists was a preferred option in this situation [3••].

Potassium-competitive acid blockers (P-CAB), a new class of acid-suppressant agents, might induce a stronger acid suppression than PPI. As PPIs, they inhibit gastric H + K+ ATPase but they exhibit a faster onset of action [4]. A randomized trial demonstrated the non-inferiority of a P-CAB, vonozapran, versus lansoprazole, to heal esophagitis [5]. Less than 10% of esophagitis recurrence was observed with vonoprazan. A prospective, single center, open label study demonstrated esophagitis healing with vonoprazan 20 mg daily for four weeks in 52 out of 60 patients (87%) with persistent erosive esophagitis and symptoms following a PPI treatment for at least eight weeks [6]. These 52 patients remained symptom free after a 24-week maintenance therapy with vonoprazan 10 mg daily. Another study evaluated the factors associated with response to vonoprazan in refractory GERD patients [7]. Based on symptom questionnaires, patients who failed to respond to PPI received vonoprazan 20 mg once daily for eight weeks. 26 out of 52 did not respond to P-CAB treatment. Dyspepsia, sleep disturbances and alcohol abstinence were associated with non-response to vonoprazan. It is important to note that a majority of studies evaluating vonoprazan were conducted in Asia where the prevalence of patients with CYP2C19 extensive metabolizer genotype is high. Contrary to PPI, the elimination of P-CAB is independent of CYP2C19 and this may explain the stronger effect of PCAB on acid suppression.

Figure 1



Therapeutic management of refractory GERD according to the cause of PPI non response.

Decreasing the number of reflux episodes

Transient lower esophageal sphincter relaxations (TLESR) represent a major mechanism of reflux, and reducing their number has been a therapeutic target for years. Currently Baclofen, a gamma-aminobutyric acid (GABA)-B receptor agonist, is the only drug available that may decrease the number of TLESR in GERD patients [8]. New drugs have been developed recently targeting the inhibition of TLESRs: so far, all have failed due to lack of efficacy or serious adverse events [9,10]. In a recent study conducted in an animal model and in patients with GERD, single oral doses of mavoglurant, a selective metabotropic glutamate receptor five antagonist, induced a significant decrease of TLESR compared to baclofen [11]. Further studies are required to confirm this efficacy and the absence of severe side effects.

Improving gastric emptying

Delayed gastric emptying might increase GERD. Thus gastric prokinetics might be helpful in a subset of GERD patients. Acotiamide is an acetyl-choline esterase inhibitor that increases gastric accommodation and accelerates gastric emptying. However, a recent study failed to demonstrate its efficacy (added to PPI) in patients with overlapping GERD and dyspepsia [12]. Prucalopride, a highly specific 5-HT4 agonist, has been commercialized in Europe for the treatment of constipation. It has been shown to decrease acid esophageal acid exposure and stimulate gastric emptying in healthy volunteers [13••], and may stimulate secondary peristalsis in GERD patients [14].

Decreasing esophageal sensitivity

Limiting the contact between the reflux content and the esophageal mucosa may help to decrease esophageal sensitivity. The antacid–alginate Gaviscon® was tested in a placebo-controlled trial in patients with persistent heartburn on PPI [15]. This study failed to demonstrate a significant difference over placebo in term of clinical response (defined as reduction in 'bad days'). It is important to note that PPI non response was assessed only on symptom occurrence.

Rikkunshito, a traditional Japanese herbal medicine might improve the barrier function and thus decrease esophageal symptoms. It was tested in 47 patients with persistent GERD symptoms on PPI and a normal upper GI endoscopy [16]. After 6–8 weeks administration of rikkunshito in addition to PPI (open label study), a significant decrease of heartburn, fullness and abdominal discomfort was observed, and quality of life was improved.

Antidepressant drugs amitriptylin and citalopram may be used to decrease visceral hypersensitivity [17]. Along with cognitive behavioral therapy, the use of these drugs was favored by experts in refractory GERD patients with reflux sensitivity and absence of hiatal hernia [3••].

Surgery and minimally invasive procedures

In patients with persistent pathological reflux on PPI, restoring a functional esophago-gastric barrier might be a