

# Proton pump inhibitor-refractory gastroesophageal reflux disease: challenges and solutions

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**Abstract:** A significant percentage of patients with gastroesophageal reflux disease (GERD) will not respond to proton pump inhibitor (PPI) therapy. The causes of PPI-refractory GERD are numerous and diverse, and include adherence, persistent acid, functional disorders, nonacid reflux, and PPI bioavailability. The evaluation should start with a symptom assessment and may progress to imaging, endoscopy, and monitoring of esophageal pH, impedance, and bilirubin. There are a variety of pharmacologic and procedural interventions that should be selected based on the underlying mechanism of PPI failure. Pharmacologic treatments can include antacids, prokinetics, alginates, bile acid binders, reflux inhibitors, and antidepressants. Procedural options include laparoscopic fundoplication and LINX as well as endoscopic procedures, such as transoral incisionless fundoplication and Stretta. Several alternative and complementary treatments of possible benefit also exist.

**Keywords:** PPI failure, resistant GERD, acid-related diseases, gastroesophageal reflux disease, acid reflux, proton pump inhibitors

## Introduction

Gastroesophageal reflux disease (GERD), the most common upper gastrointestinal (GI) disorder in the US,<sup>1</sup> is defined as symptoms or lesions that result from the retrograde flow of gastric contents into the esophagus.<sup>2</sup> Proton pump inhibitors (PPIs), after acid activation to sulfonamides, covalently bind to cysteine residues on the luminal surface of H<sup>+</sup>/K<sup>+</sup> ATPase proton pumps in the parietal cells, blocking ion transport and acid secretion. Chemically, all PPIs consist of a benzimidazole ring and a pyridine ring but vary in side ring substitution.<sup>1</sup> Although PPIs are currently the most effective treatment for GERD and its complications,<sup>3</sup> up to 40% of patients with nonerosive reflux disease (NERD) remain symptomatic on standard therapy, and approximately 10–15% of patients with erosive esophagitis (EE) do not achieve full remission after 8 weeks of treatment.<sup>4,5</sup>

Patients with continued symptoms despite PPI treatment are considered to have refractory GERD, which is generally defined as the persistence of typical symptoms that do not respond to stable, twice-daily PPI dosing during at least 12 weeks of treatment.<sup>6–8</sup> Up to 30% of GERD patients experience refractory GERD.<sup>2</sup>

## Causes of refractory GERD

There are many potential causes of refractory GERD that vary in incidence, clinical importance, and symptom severity and frequency. Poor compliance and adherence should first be assessed before further evaluation is pursued. The most common

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mechanisms for refractory GERD include functional bowel disorders, weakly acidic reflux, and residual acid. Factors related to metabolism and bioavailability play a limited role in PPI failure. GERD-like symptoms may also be due to a variety of other disorders, such as eosinophilic esophagitis (EoE), pill-induced esophagitis, infectious esophagitis, and achalasia, which should be considered in the differential diagnosis of patients with unremitting symptoms (Table 1).

## Factors related to medication administration

### PPI adherence and compliance

An important initial consideration for all patients not fully responding to PPI therapy is to evaluate medication adherence, as regular medication administration is crucial for maximal efficacy. Several studies indicate poor medication adherence among PPI users, with two reports finding that only 53.8% and 67.7% of patients filled their monthly PPI prescription more than 80% of the time.<sup>9,10</sup> Moreover, many patients discontinue PPIs when their symptoms resolve, as demonstrated by a large population-based survey in which only 55% of patients took a PPI once daily for 4 weeks as prescribed, with 37% taking it for 12 or fewer days out of the month.<sup>11,12</sup>

Medication compliance is also important to investigate, as several studies show that patients do not use PPIs at the appropriate time. One study of 100 patients with persistent GERD symptoms found that only 8% of patients reported dosing at the optimal 30–60 minutes prior to meal.<sup>13</sup> Common reasons for nonadherence and noncompliance include absence of symptoms, personal preference, side effects, and lack of knowledge or misinformation about medication,<sup>14</sup> as demonstrated by one national survey that 36% of physicians give their patients no directions or incorrect directions

regarding mealtime dosing of PPIs, 26% give no instructions or say that timing is unimportant, and 10% incorrectly advise their patients to take them with or after food.<sup>15</sup>

### Choice of agent

Limited data directly compares the efficacy of different PPIs. Although some studies suggest that certain PPIs may be more effective for GERD, this is not supported by a meta-analysis of pooled data.<sup>16</sup> Therefore, choice of agent is an unlikely cause of refractory GERD.

## Factors associated with functional esophageal disorders

Functional GI disorders have traditionally been defined as symptomatic disorders without known structural, metabolic, or infectious cause.<sup>17</sup> Functional disorders likely result from a diverse group of underlying mechanisms, which may include increased mucosal sensitivity to mechanical and chemical stimulation or worsened central perception of pain.<sup>18</sup>

### Functional heartburn

Rome IV defines functional heartburn as 3 months of burning retrosternal pain without evidence of continued reflux or underlying motility disorder that is not relieved by optimal antisecretory therapy.<sup>18</sup> As many as 58% of patients with refractory GERD fall into this category.<sup>19,20</sup>

### Esophageal hypersensitivity

Esophageal hypersensitivity, which is defined as the heightened perception of various stimuli, including acid, temperature, mechanical distention, and electrical stimulation,<sup>21</sup> may contribute to persistent GERD symptoms despite PPI therapy. The mechanism of esophageal hypersensitivity is unclear but likely involves both peripheral and central sensitization via dilated intracellular spaces (DISs) and exposure of subepithelial nerves to acid.<sup>22–24</sup> Esophageal hypersensitivity may also be influenced by stress, which can alter brain processing of sensation, autonomic nervous activity, cortisol release, and pathways involved in the spinal transmission of nociceptive signals.<sup>22</sup>

Although the role of esophageal hypersensitivity in PPI failure has not been well studied, most treatment-refractory patients demonstrate a lower threshold for pain perception with esophageal balloon distention or electrical stimulation.<sup>25</sup> Studies of patients with GERD who have been exposed to anxiety induction or acute auditory stress show increased perceptual response to acid exposure and exacerbation of

**Table 1** Causes of refractory GERD

- PPI adherence and compliance
- Functional esophageal disorders
  - Functional heart burn, esophageal hypersensitivity, IBS
- Weakly acidic or nonacid reflux
  - Weakly acid reflux, duodenogastroesophageal reflux
- Residual acid
  - NAB, acid pocket
- Delayed gastric emptying
- Rapid PPI metabolism
- Eosinophilic esophagitis
- Causes unrelated to GERD

**Abbreviations:** GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; IBS, irritable bowel syndrome; NAB, nocturnal acid breakthrough.

symptoms.<sup>26,27</sup> Further supporting the contribution of esophageal hypersensitivity to refractory GERD, DIS has been shown to resolve in patients who respond to PPI therapy<sup>28,29</sup> but persist in those who remain symptomatic.<sup>30,31</sup>

## Factors affecting functional esophageal disorders

### Psychological comorbidity

Data on the contribution of psychological comorbidity to refractory GERD are mixed. Several studies have shown that patients with GERD, particularly those with NERD, have a high prevalence of psychiatric disease and psychosocial stressors.<sup>32–37</sup> In a recent analysis of PPI therapy in patients with psychological distress, high baseline levels of anxiety and depression, and decreased general well-being, predicted lower treatment response.<sup>38</sup> Another study similarly found that comorbid psychological distress was independently associated with more severe baseline GERD symptoms, greater residual symptoms, and worse disease-specific quality of life both before and after PPI therapy.<sup>39</sup> Sleep dysfunction and a history of either psychotherapy or psychiatric medication have also been significantly associated with poor PPI response.<sup>40</sup>

In contrast to these findings, however, a recent prospective study of GERD patients receiving once- or twice-daily PPI therapy found that poor treatment response was not associated with anxiety or depression.<sup>41</sup> A study of GERD patients in a primary care setting similarly revealed that the relative risk of anxiety or depression in PPI failure was minimal, with an odds ratio of 1.15.<sup>42</sup>

The reported relationship between PPI failure and psychological distress is multifactorial. Psychiatric disease may compromise esophageal motor function by affecting the enteric nervous system.<sup>32,43,44</sup> Some studies suggest that reflux symptoms may be affected by substance use<sup>45</sup> and psychiatric medications, such as benzodiazepines, which can decrease lower esophageal sphincter (LES) pressure,<sup>46</sup> and tricyclic antidepressants (TCAs), which block cholinergic receptors and may compromise acid clearance.<sup>47</sup> Sleep disturbance has also been associated with greater severity of reflux symptoms and poorer response to treatment.<sup>22</sup>

Psychological comorbidity may also affect perception of treatment success. In the setting of acute stress, patients report increased severity and frequency of GERD symptoms regardless of alteration in esophageal acid exposure. In a study of laparoscopic antireflux surgery for treatment-refractory GERD, patients with coexisting major depressive disorder were more likely to report residual symptoms despite improvements on objective assessment scores.<sup>48</sup>

A prospective controlled trial of patients undergoing a laparoscopic Nissen fundoplication similarly found that patients with refractory GERD symptoms had a significantly higher level of somatization.<sup>49</sup>

### Irritable bowel syndrome

The overlap between GERD and irritable bowel syndrome (IBS) has been recognized for more than 20 years, with up to 71% of GERD patients reporting IBS symptoms.<sup>50,51</sup> The association between IBS and GERD is thought to result from either common underlying mechanisms or symptoms.<sup>52</sup>

Data is limited, but studies have shown that concomitant IBS predicts poorer treatment response in patients with GERD. In one prospective, open-label study, patients with GERD and IBS-like symptoms showed reduced response rates to pantoprazole when compared to patients without IBS-like symptoms.<sup>52</sup> Another study similarly found that comorbid IBS was associated with increased GERD symptoms and lower quality of life both before and after PPI treatment, although this may reflect more severe baseline symptoms that are less responsive to treatment.<sup>39</sup>

## Weakly acidic or nonacid reflux

### Weakly acidic reflux

Weakly acidic reflux is defined as a reflux event in which the esophageal pH falls by at least one unit but not below four.<sup>53</sup> The exact mechanism through which weakly acid reflux produces symptoms remains unclear, but several theories have been proposed based on the volume or content of refluxate. A large volume of weakly acidic refluxate may cause mechanical dilation of the esophagus and induce reflux symptoms, as demonstrated by studies in which direct mechanical balloon dilation of the esophagus causes heartburn sensation.<sup>54,55</sup> GERD symptoms can also result from bile acids, which may be contained in weakly acidic reflux.<sup>56</sup> The proteolytic effect of pepsin, which can be introduced into the esophagus during a weakly acidic reflux event, may also contribute to refractory symptoms. While pepsin is maximally active at a pH of 1.9–3.6, it maintains some activity up to a pH of 6. Additionally, pepsin maintains its structure up to a pH of at least 7.5 and can be reactivated by a subsequent acid reflux event or acidic meal.<sup>57</sup> Esophageal healing may also be compromised because the restoration and regeneration of the mucosa are inhibited at pH <6.5.<sup>57</sup> Finally, previous exposure of the esophagus to acid can lead to subsequent hyperalgesia to both mechanical and chemical stimulation.<sup>58–60</sup> Additionally, patients with PPI-refractory GERD have been found to have slower esophageal clearance,<sup>61</sup> which may exacerbate all the above mechanisms.

The clinical significance of weakly acidic reflux in refractory GERD remains unclear. Although multiple studies show that only a minority of weakly acidic reflux events occur at the same time as refractory symptoms, a wide range (16.7–40%) is reported.<sup>19,62–65</sup>

### Duodenogastroesophageal reflux (DGER)

DGER refers to reflux of duodenal contents, including bile, through the stomach and into the esophagus.<sup>66</sup> Esophageal bilirubin exposure can occur with or without weakly acidic reflux<sup>67</sup> and lead to decreased esophageal mucosal integrity<sup>56</sup> through epithelial cell apoptosis, DIS, and increased mucosal permeability.<sup>68,69</sup> In one study of refractory GERD, DGER was found in 88% of PPI nonresponders and only 27% of responders.<sup>7</sup> Another study similarly found that 64% of patients with GERD who did not respond to standard-dose PPI therapy had pathologic DGER.<sup>70</sup>

### Delayed gastric emptying

In refractory GERD, the role of delayed gastric emptying, which should theoretically lead to larger or more frequent reflux events, remains unclear. One study of 66 patients with refractory GERD who underwent gastric emptying studies found no statistical difference between patients with gastroparesis and controls with respect to total number or duration of acid and nonacid reflux events.<sup>71</sup> However, a smaller study found that after 8 weeks of PPI treatment, patients with persistent symptoms and EE had more abnormal gastric emptying as compared to patients with persistent EE but no symptoms.<sup>72</sup> A possible association between gastric emptying and refractory GERD was also demonstrated in a small study in which 88% of patients who experienced improvement in gastroparesis symptoms also reported reduced GERD symptoms.<sup>73</sup>

## Residual acid

### Acid pocket

Postprandially, there can exist an area of highly acidic gastric juice at the esophagogastric junction, termed an acid pocket, which contains newly secreted acid that does not mix with food and so remains unbuffered. This pocket may migrate into the esophagus and cause postprandial reflux symptoms.<sup>74</sup> While PPI use may alter the location or reduce the size of the pocket,<sup>75</sup> one of the only studies investigating this mechanism found no difference in location or pH of the acid pocket between PPI responders and partial responders.<sup>21</sup>

### Nocturnal acid breakthrough (NAB)

NAB is defined as a gastric pH <4 for at least 1 hour during the night in patients on PPI therapy.<sup>5</sup> While NAB is very common, occurring in as many as 75% of patients on twice-daily PPI therapy,<sup>76</sup> it likely does not play a role in the pathogenesis of resistant GERD. In one study of refractory GERD, 37 of 52 patients were found to have NAB, but only 17 had concurrent GERD symptoms. Additionally, there were a similar number of symptoms in patients with and without NAB.<sup>77</sup> Another study found that adding ranitidine to twice-daily omeprazole did not improve nocturnal heartburn symptoms or sleep quality despite reductions in NAB.<sup>78</sup>

## Metabolism and bioavailability

### Rapid PPI metabolism

PPIs are metabolized in the liver by cytochrome P450 2C19 (CYP2C19) and to a much lesser extent by cytochrome P450 3A4.<sup>79</sup> As a result of genetic polymorphisms, CYP2C19 exists as three possible genotype groups with varying metabolic activity: homozygous extensive metabolizers (carrying two mutated alleles), heterozygous extensive metabolizers (carrying one mutant and one wild-type allele), and poor metabolizers (carrying two wild-type alleles).<sup>79</sup> There is a significant ethnic variation in the distribution of these alleles, as up to 70% of Caucasians, compared to 30–40% of Asians, are extensive metabolizers.<sup>80</sup>

Extensive metabolizers are expected to show decreased acid suppression in response to PPI therapy because more rapid elimination leads to decreased mean residence time and area under the curve. The area under the curve for poor metabolizers is reportedly 5–12 times higher than in extensive metabolizers.<sup>81</sup> A recent meta-analysis found that PPI response rate in GERD among rapid metabolizers, intermediate metabolizers, and poor metabolizers was 52.2%, 56.7%, and 61.3%, respectively.<sup>82</sup>

The impact of CYP2C19 activity on refractory GERD symptoms remains unclear, as nearly all studies use standard rather than double-dose PPI therapy.<sup>82</sup> There is only one study examining the difference in response rate between extensive and poor metabolizers on both standard and twice-daily pantoprazole. After 8 weeks of therapy, sustained symptom response (SSR) did not differ between poor metabolizers who were receiving either dose of pantoprazole. Heterozygous extensive metabolizers showed an SSR of 94.9% on twice-daily dosing but only 73.7% on standard dosing. Similarly, homozygous extensive metabolizers showed an SSR of 82.1% on twice-daily dosing as compared to 68.4%

on standard dosing.<sup>83</sup> The discrepancy between response rate of double- and standard-dose PPI among extensive metabolizers suggests that PPI metabolism may play an important role in refractory GERD.

### PPI resistance

A single abstract from 1995 proposed that mutations in cysteine residues of the alpha subunit of the proton pump may inhibit omeprazole binding and lead to PPI resistance, although the two patients evaluated were not found to have such mutations.<sup>84</sup> No further studies have ever identified mutations leading to PPI resistance, suggesting that it does not play a role in refractory GERD.

## Other differential diagnostic considerations

### Eosinophilic esophagitis

The relationship between GERD and EoE, a chronic, immune-mediated disease characterized by symptoms of esophageal dysfunction and eosinophilic inflammation, is complex. Distinguishing EoE from GERD is challenging, as both conditions involve heartburn, chest pain, dysphagia, and esophageal eosinophilia,<sup>85</sup> which may respond to PPIs.<sup>86</sup> Currently, it is unclear if GERD and EoE exist independently or one may cause the other.<sup>85</sup> Further complicating this relationship is new data suggesting that PPIs may predispose patients to developing EoE by altering mucosal immune responses and increasing exposure to food allergens (Table 2).<sup>86</sup>

The reported prevalence of EoE in patients with refractory GERD is limited and variable, with estimates ranging from 1% to 15%.<sup>87–90</sup> In one study of 130 patients with persistent heartburn and/or regurgitation despite receiving 6 weeks of omeprazole treatment, only one patient was found to have

lesions on upper endoscopy suggestive of EoE.<sup>89</sup> Similarly, a study of 105 patients with PPI-resistant heartburn found that only 0.9% of patients had EoE on upper endoscopy.<sup>90</sup> Overall, EoE is a relatively uncommon disorder and unlikely to be a cause of GERD symptoms that do not respond to PPI therapy.<sup>91</sup>

### *Helicobacter pylori* status

Studies show that PPIs are actually more effective in the setting of *Helicobacter pylori* infection. In patients with *H. pylori*, PPI treatment results in a higher intragastric pH,<sup>92</sup> higher rates of healing of EE, and improvement of GERD symptoms.<sup>93</sup> It is unclear if *H. pylori* eradication leads to worsening of GERD symptoms, as several small studies have found conflicting results.<sup>94</sup>

### Delayed healing

A meta-analysis of patients with EE showed that PPIs result in healing rates and symptom response that are twice that of histamine 2 receptor antagonists (H2RAs). On PPIs, complete heartburn relief occurs at a rate of 11.5% per week. More significant disease, Los Angeles class C and D, might take longer. However, this study did not explicitly investigate the association between persistent GERD symptoms and incompletely healed EE.<sup>4</sup> Additional data is needed to determine if delayed healing significantly contributes to resistant GERD.

### Barrett's esophagus (BE)

BE is more prevalent in patients with GERD symptoms<sup>95</sup> but does not appear to play a large role in PPI resistance, as the vast majority (80–85%) of patients with BE have full resolution of GERD symptoms with PPI therapy.<sup>5</sup>

### Causes unrelated to GERD

Other diseases that are associated with heartburn should be considered in patients with refractory GERD. These include achalasia, Zollinger–Ellison syndrome, pill-induced esophagitis, autoimmune skin disease with esophageal manifestations,<sup>96</sup> infectious esophagitis (such as candida and herpes simplex virus),<sup>97</sup> esophageal cancer,<sup>98</sup> nonsteroidal anti-inflammatory drug use,<sup>99</sup> rumination syndrome,<sup>100</sup> radiation-induced esophagitis,<sup>101</sup> and ingestion of caustic agents.<sup>102</sup> The mechanisms of these insults make them unlikely to respond to PPI therapy.

## Diagnosis

A standard evaluation of refractory GERD symptoms should include a thorough symptom evaluation, structural evaluation

**Table 2** Causes unrelated to GERD

- Eosinophilic esophagitis
- Achalasia
- Zollinger–Ellison syndrome
- Pill-induced esophagitis
- Autoimmune skin diseases with esophageal manifestations
- Rumination syndrome
- Infectious esophagitis
- Esophageal cancer
- NSAID use
- Radiation-induced esophagitis
- Caustic agent ingestion

**Abbreviations:** GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug.

of the upper GI tract, and a functional evaluation to include assessing the nature of the refluxed material and possibly esophageal motor function (Table 3).

## Symptom evaluation

The first step in evaluating refractory GERD is clarification of persistent symptoms and aggravating factors. Patients with refractory GERD usually report atypical burning in the upper chest or throat that is unrelated to meals and associated with belching, dyspepsia, and bloating.<sup>103</sup> Regurgitation, or the backflow of gastric contents into the chest or mouth,<sup>104,105</sup> is also common in refractory GERD but may be a sign of gastroparesis or rumination syndrome.<sup>106</sup> Alarm symptoms, such as anorexia, dysphagia, odynophagia, weight loss, anemia, and GI bleeding, must also be evaluated, as they may indicate more severe disease, such as stricture formation<sup>107</sup> or upper GI malignancy.<sup>108</sup>

## Upper GI series/barium swallow

Barium radiographs can be used to evaluate patients with esophageal symptoms, but the sensitivity of this test is extremely low.<sup>109</sup> There is no role for barium swallow in the routine diagnosis of GERD, but it may be useful in the setting of dysphagia.<sup>110,111</sup>

## Upper GI endoscopy

The American Society of Gastrointestinal Endoscopy recommends upper GI endoscopy for patients with persistent GERD symptoms despite optimization of PPI therapy.<sup>112</sup> When endoscopy is performed, biopsies should be obtained to rule out EoE<sup>22</sup> and esophageal cancer.<sup>113</sup> Endoscopy can also identify alternative causes of refractory symptoms, such as infectious esophagitis, caustic ingestion, BE, esophageal cancer, or gastric or duodenal ulcer.<sup>114</sup>

## Esophageal pH monitoring

Esophageal pH monitoring is a common diagnostic tool for evaluating patients with treatment-refractory GERD. While the diagnostic yield of pH monitoring in patients on PPI therapy is low, it can identify refractory GERD patients

who might benefit from further PPI therapy and those whose symptoms are not related to residual acid reflux. Esophageal pH testing in patients with atypical symptoms who are off of treatment can determine if reflux is the cause of their initial symptoms.<sup>98</sup>

A wireless pH capsule is often used because it is more comfortable and can capture pH for several days.<sup>115</sup> However, the value of extended pH monitoring remains unclear, as a recent study found that 67% of refractory GERD patients had normal pH testing throughout 2 days of monitoring.<sup>116</sup> Moreover, given their inability to measure weakly acidic or alkaline reflux, both wireless and traditional pH monitoring have been replaced by esophageal impedance and pH monitoring.<sup>117</sup>

## Esophageal multichannel intraluminal impedance–pH monitoring

In esophageal multichannel intraluminal impedance–pH monitoring, an intraluminal probe is placed in the esophagus with electrodes at multiple levels. Because air has a high impedance and liquid has a low impedance, both the composition and the proximal extent of a reflux event can be measured.<sup>114</sup> A pH monitor on the impedance catheter also allows the acidity of the reflux to be characterized.<sup>104</sup> Therefore, unlike esophageal pH monitoring alone, intraluminal impedance monitoring can identify reflux as acidic, weakly acidic, or alkaline, and its composition as liquid, gas, or both.

## Esophageal Bilitec

Bilitec utilizes a sensor mounted on a catheter to detect the presence of bilirubin in the distal esophagus as a marker for bile reflux.<sup>118</sup> The addition of Bilitec to pH monitoring has been shown to clarify the composition of reflux<sup>70</sup> and increase the rate of abnormal results by 30–40% in treatment-refractory patients.<sup>119</sup> It is not widely available and requires specific dietary restrictions.<sup>114</sup>

## Esophageal manometry

Esophageal manometry in refractory GERD has limited benefit because most patients with treatment failure have NERD or a functional bowel disorder.<sup>5</sup> However, esophageal manometry can be used for positioning sensors prior to pH monitoring and for ruling out esophageal motor disorders or achalasia.<sup>22</sup> Manometry is also important for patients who are considering antireflux surgery, as up to 40% of patients with preoperative peristaltic dysfunction experience postoperative dysphagia.<sup>120</sup>

**Table 3** Diagnostic tools

- Upper GI series
- Upper GI endoscopy
- Esophageal pH monitoring
- Esophageal impedance monitoring
- Esophageal Bilitec monitoring
- Esophageal manometry

**Abbreviation:** GI, gastrointestinal.

## Treatment

There are a myriad of potential therapies that vary in efficacy, invasiveness, and accessibility. Most therapeutic strategies target one or more of the abovementioned underlying mechanisms (Table 4).

### Lifestyle modification

Lifestyle modifications, such as elevation of the head of the bed at night, weight loss, and avoidance of alcohol, tobacco, caffeine, coffee, citrus, chocolate, and high-fat or spicy foods, are often recommended as first-line therapy for GERD despite poor evidence supporting their use.<sup>121</sup> A meta-analysis found that GERD improved with weight loss and head elevation but not with dietary interventions or abstinence from tobacco or alcohol.<sup>121</sup>

## Pharmacologic treatments

### Double-dose PPI

Resistant GERD is generally defined as persistent symptoms despite twice-daily PPI dosing.<sup>6-8</sup> However, for patients who fail once-daily PPI therapy, the standard of care in clinical practice is to double the dose<sup>5</sup> to twice-daily dosing before breakfast and dinner.

### Choice of agent

There is limited data suggesting that one PPI agent is superior to another for refractory GERD. However, if the reason for PPI failure is poor compliance, one possible solution may lie in choice of PPI. Dexlansoprazole MR, for example, employs a novel dual delayed-release formulation that allows for once-daily dosing without regard to time of day or food consumption.<sup>1</sup>

### PPI + H2RA

H2RAs are often added to PPI therapy to control nocturnal GERD symptoms, as nocturnal acid secretion is mainly

driven by histamine and is therefore less responsive to PPI therapy.<sup>104</sup> The addition of a nighttime H2RA to twice-daily PPI has been shown to decrease NAB from 64% to 17%<sup>122</sup> and improve both day- and nighttime GERD symptoms.<sup>123</sup> However, tachyphylaxis to the acid-lowering effects of H2RAs can develop in as little as 1 week,<sup>124</sup> suggesting their use may be of limited utility in resistant GERD.

### PPI + prokinetic

Prokinetics, a group of drugs that increase esophageal and gastric motility, may be useful for patients whose refractory symptoms result from poor esophageal clearance. Prokinetics act at a variety of receptors, including 5-hydroxytryptamine (5-HT) 4, dopamine 2 (D2), motilin, and ghrelin.<sup>136</sup> A recent meta-analysis found that the addition of a prokinetic to a PPI showed no benefit in symptom control but improved quality of life.<sup>126</sup> Side effects, including fatigue, cardiac events, tardive dyskinesia, and tremor, have limited their use.<sup>127</sup>

### Metoclopramide

Metoclopramide is a D2 receptor antagonist and 5-HT4 agonist that increases LES pressure and accelerates gastric emptying.<sup>128</sup> Its use is often limited by significant side effects including tardive dyskinesia, agitation, and insomnia.<sup>129</sup> The only study of metoclopramide for refractory GERD found that its use with an H2RA did not improve symptoms over the H2RA alone.<sup>130</sup> Additional studies are needed to assess the use of metoclopramide in conjunction with a PPI for resistant GERD.

### Cisapride

Cisapride is a 5HT4 agonist<sup>2</sup> that increases lower esophageal pressure, enhances esophageal acid clearance, and promotes gastric emptying.<sup>131</sup> In one study, cisapride in conjunction with an H2RA was found to be superior to an H2RA alone for the treatment and maintenance of heartburn symptoms.<sup>131</sup> However, the addition of cisapride to omeprazole does not appear to improve symptom control.<sup>2</sup> Cisapride was removed from the market in 2000<sup>132</sup> due to severe cardiac complications including QT prolongation, arrhythmia, and death.<sup>133</sup> Cisapride only remains available through a limited access protocol for investigational purposes or patients who have failed all other treatments.<sup>134</sup>

### Alginates

Alginates, or anionic polysaccharides, such as Gaviscon, have been shown to localize to the acid pocket,<sup>135</sup> where they precipitate into a low-density, pH-neutral viscous gel

**Table 4** Treatment

- Lifestyle modification
  - Weight loss, diet
- Medications
  - Antacids, motility agents, antidepressants, reflux inhibitors
- Endoscopic procedures
  - TIF, MUSE, Stretta
- Surgery
  - Fundoplication
- Alternative and complementary therapies
  - Acupuncture, herbal treatments

**Abbreviations:** TIF, transoral incisionless fundoplication; MUSE, Medigus ultrasonic surgical stapler.

that floats on top of stomach contents and impedes reflux.<sup>136</sup> The combination of omeprazole and sodium alginate has been shown to significantly improve symptoms at 4 weeks compared to omeprazole alone.<sup>148</sup>

### Sucralfate

Sucralfate is a mucosal protectant that binds to inflamed tissue and blocks the diffusion of gastric acid and pepsin across the esophageal mucosa, thereby inhibiting the erosive effects of pepsin and potentially bile.<sup>137</sup> Sucralfate also stimulates growth factors that promote mucus and bicarbonate formation as well as ulcer healing.<sup>137</sup> Compared with H2RAs and alginates with antacids, sucralfate is equally effective in controlling GERD symptoms associated with EE but has only been shown to heal esophageal mucosa in low-grade EE.<sup>138,139</sup> Sucralfate is rarely used given its four times daily dosing and limited efficacy compared with PPIs but is more commonly prescribed in pregnant women, as it is not associated with maternal or fetal adverse events.<sup>140</sup> Currently, there is no data on the role of sucralfate in patients who do not respond to PPI therapy.<sup>141</sup>

### Bile acid binder

Bile acid binders, such as cholestyramine and colesevelam, should theoretically decrease bile acid reflux. However, there is no data for or against their use in PPI-resistant GERD.<sup>5</sup>

### Reflux inhibitors

Distention of the proximal stomach causes a vagal-mediated relaxation of the LES, allowing reflux to occur.<sup>2</sup> Reflux inhibitors that inhibit this relaxation are likely to be of the most benefit to patients whose symptoms are due to weakly acidic reflux or DGER.<sup>2</sup>

### Baclofen

In patients with GERD, Baclofen, a GABA-B receptor agonist, has been shown to decrease transient LES relaxation by 40%, increase LES pressure, and reduce the rate of reflux events.<sup>142</sup> Most studies show that Baclofen monotherapy is effective for GERD.<sup>143</sup> The only study that examined its use as an add-on to PPI therapy for GERD found no difference in symptoms, although this result is unsurprising given that the study was performed on patients with well-controlled GERD.<sup>144</sup> A small study of patients with confirmed DGER and persistent symptoms despite PPI treatment found that the addition of baclofen 20 mg three times daily leads to a significant reduction in duodenogastric reflux episodes and improvement in symptoms.<sup>145</sup> The effect of baclofen on the

central nervous system results in side effects such as dizziness, weakness, and fatigue, although these may be limited with nighttime dosing.<sup>146</sup>

### Antidepressants

TCA, selective serotonin reuptake inhibitors (SSRIs), and trazodone can potentially improve esophageal pain in patients with visceral hypersensitivity. These agents are thought to confer visceral analgesia by acting at the central nervous system and/or sensory afferents level.<sup>147</sup> Data is strongest for the efficacy of SSRIs in acid-sensitive esophagus and functional heartburn. In a controlled trial of patients with acid-sensitive esophagus, citalopram 20 mg daily was superior to placebo in improving regurgitation, heartburn, and chest pain.<sup>148</sup> A study of 144 patients with refractory GERD similarly found that fluoxetine, compared with placebo and omeprazole, led to greater reductions in heartburn, and was particularly effective for patients with functional heartburn and hypersensitive esophagus.<sup>149</sup> Controlled trials of nortriptyline do not support its use for heartburn symptoms,<sup>150,151</sup> although observations of TCAs in healthy subjects suggest that they can decrease esophageal hypersensitivity.<sup>152,153</sup> One hypothesis for the discrepancy between TCA and SSRI trials is that TCAs prolonged orocecal times, whereas SSRIs reduce them, potentially decreasing the window in which reflux can occur.<sup>154</sup> Trazodone, a serotonin antagonist and reuptake inhibitor, has also been effective for relieving chest pain, dysphagia, heartburn, and regurgitation secondary to esophageal contraction abnormalities.<sup>44</sup>

## Procedures

### Laparoscopic fundoplication

Antireflux surgery can be considered for patients who either fail PPI therapy or have complications of reflux, such as severe esophagitis, stricture, or risk of aspiration. Surgery may also be appropriate for patients who cannot tolerate or comply with long-term pharmacotherapy. The primary surgical intervention for the treatment of GERD is laparoscopic fundoplication. Although some case series have shown that antireflux surgery improves symptoms for patients with refractory GERD,<sup>155,156</sup> larger peer-reviewed and controlled studies suggest that surgery is primarily effective for patients who have a history of partial or complete response to PPI therapy.<sup>157-159</sup> Outcomes from surgery are also superior for patients with typical symptoms who have objective evidence of acid reflux and good presurgical compliance with antireflux medications.<sup>160,161</sup> Potential adverse effects of laparoscopic fundoplication include dyspepsia,



dysphagia, and gas bloat syndrome,<sup>2</sup> as well as recurrence of symptoms.<sup>162</sup> Given the limitations and possible side effects of antireflux surgery, all surgical candidates should undergo a thorough assessment of symptoms and reflux monitoring off of PPI treatment.<sup>2</sup>

## Endoscopic procedures

### Stretta

Stretta improves refractory GERD symptoms by delivering radiofrequency energy to the LES, leading to increased basal pressure and reduced compliance.<sup>163</sup> Stretta has been shown to improve the antireflux barrier<sup>164</sup> as well as decrease refluxate volume,<sup>165</sup> intraesophageal pH,<sup>166</sup> and esophageal acid exposure.<sup>163</sup> In a recent open-label trial of Stretta, 72% of patients with refractory GERD showed normalization of GERD health-related quality-of-life (HRQL) scores, and 41% reported complete discontinuation of PPI therapy at 10-year follow-up.<sup>163</sup> However, data is mixed, with a recent systematic review showing no significant benefit over placebo.<sup>167</sup> Clinical use was previously limited by concerns for esophageal perforation, but more recent studies indicate that the most common side effect is transient chest pain that does not require treatment.<sup>168</sup>

### Transoral incisionless fundoplication (TIF)

TIF is performed using the EsophyX device inserted transorally with the endoscope. EsophyX allows for creation of a fundoplication at the level of the gastroesophageal junction.<sup>168</sup> Although limited, long-term data suggests that TIF may be effective for symptom control and decreased PPI use for 2–6 years. There is no evidence that TIF is more effective than laparoscopic Nissen fundoplication, but two recent studies demonstrated that TIF is superior to high-dose PPI therapy for controlling heartburn and regurgitation at 6-month follow-up.<sup>169,170</sup> TIF may be most helpful for patients with hiatal hernias <2 cm and Hill Grade I/II valves.<sup>171</sup>

## Novel procedures

### LINX

The LINX is a magnetic augmentation device that is surgically positioned around the LES. It was approved by the FDA in 2012 for severe, refractory GERD symptoms that do not respond to alternative treatments.<sup>2,172</sup> Data is limited to short-term case series,<sup>172</sup> but multiple prospective studies have demonstrated the safety and efficacy of LINX in treating patients with refractory GERD symptoms.<sup>173–175</sup>

## LES electrical stimulation therapy

Another novel procedure for refractory GERD is LES electrical stimulation therapy (EST), which has been used for treating GI motility disorders. The LES stimulation system consists of an implantable pulse generator (IPG), a bipolar lead with two electrodes, and an external programmer. The IPG generates electrical stimulation to the LES 8–12 times per day for 30 minutes per session.<sup>176</sup> Stimulation of the LES in patients with GERD has been shown to increase resting LES pressure without affecting peristalsis or LES relaxation.<sup>177</sup> Although studies demonstrate that EST is safe and effective for refractory GERD at both 1- and 2-year follow-ups,<sup>178,179</sup> data is restricted to short-term case series and open-label studies, and further research into the mechanism of action is needed.<sup>177</sup>

## Medigus ultrasonic surgical stapler (MUSE)

The MUSE is an endoscopically inserted device that can be used to form a skin flap within the esophagus similar to TIF.<sup>180</sup> The fundoplication is created transorally using a surgical stapler that is guided by video and ultrasound.<sup>181</sup> A multicenter prospective trial found that at a 6-month follow-up, 73% of patients showed a significant improvement in GERD-HRQL score, with 65% of patients completely discontinuing PPI use.<sup>181</sup> The first 24 patients treated with MUSE suffered several adverse events including pneumomediastinum, GI hemorrhage, and empyema formation.<sup>181</sup> However, after a redesign of the procedural protocol and the device itself, no further serious adverse events were reported. A 4-year follow-up found no new adverse events, but that the portion of patients who remained off daily PPI had decreased from 84% to 69%.<sup>182</sup>

## Nonpharmacologic interventions

### Cognitive behavioral therapy (CBT)

While controlled trials investigating the effects of CBT on refractory GERD are needed, data on noncardiac chest pain,<sup>183–185</sup> as well as a large literature supporting the efficacy of CBT in reducing chronic pain,<sup>186</sup> suggests that CBT may be helpful for managing symptoms.

### Hypnotherapy

Hypnotherapy has demonstrated efficacy for IBS,<sup>187</sup> functional dyspepsia,<sup>188</sup> noncardiac chest pain,<sup>189,190</sup> globus sensation,<sup>191</sup> and heartburn.<sup>192</sup> Studies have also shown that hypnotherapy can influence gastric acid secretion,<sup>193</sup> gastric emptying time,<sup>194</sup> and reflux symptoms.<sup>195</sup> Hypnotherapy is

thought to affect these conditions by modulating esophageal hypervigilance, a psychological process that develops through operant conditioning in patients who have unpredictable symptoms that are misattributed to certain triggers. Decreasing esophageal hypervigilance through hypnotherapy can help with behavioral avoidance, anxiety, and coping skills, which contribute to refractory symptoms.<sup>192</sup>

### Biofeedback

Biofeedback employs visual and audio signals, as well as direct verbal feedback, to increase awareness of physiological functions. Although biofeedback has been effective for a variety of medical conditions, evidence supporting its use for GERD symptoms is limited.<sup>196</sup> One prospective uncontrolled trial found that 7 of 12 patients with functional heartburn and functional chest pain refractory to acid suppression experienced symptom improvement for up to 9 months after using biofeedback to learn abdominal breathing exercises and muscle relaxation.<sup>197</sup> Two case reports have similarly demonstrated that biofeedback can be used to teach patients how to contract and relax their abdominal muscles, leading to improvement in pH score and LES pressure, and decreasing number of reflux events.<sup>198,199</sup> The use of biofeedback is limited by the need for staff training and patients who are motivated to attending multiple sessions and continue to practice techniques.

### Alternative and complementary treatments

#### Acupuncture

While the exact mechanism by which acupuncture improves GERD symptoms is unknown, proposed mechanisms include improved gastric motility and esophageal peristalsis, and decreased visceral hypersensitivity and LES relaxation.<sup>127</sup> One randomized study of 30 patients with continued symptoms despite standard-dose PPI found that 10 sessions of acupuncture for 4 weeks experienced a significant improvement in day and nighttime heartburn as well as acid regurgitation.<sup>200</sup>

#### Transcutaneous electrical acustimulation (TEA)

TEA is the administration of pulses of electricity to acupoints on the arm or leg. One small, placebo-controlled study of 20 patients with refractory GERD found statistically significant improvements in LESP and symptom control for patients receiving twice-daily TEA for 4 weeks.<sup>201</sup> TEA is also reported to reduce visceral hypersensitivity in IBS<sup>202</sup> and improve functional dyspepsia.<sup>203</sup>

#### Rikkunshito

Rikkunshito is a traditional Japanese remedy that is composed of eight crushed herbs.<sup>204</sup> It has been shown to affect nitric oxide-mediated gastric emptying,<sup>205</sup> increase plasma ghrelin levels,<sup>206</sup> and bind bile acids.<sup>207</sup> Despite the widespread use of rikkunshito in Japan for a variety of GI problems,<sup>204</sup> a recent study of healthy volunteers found no effect on gastric reflux or esophageal motility.<sup>208</sup> However, a prospective randomized trial comparing rikkunshito with rabeprazole to double-dose rabeprazole found a similar symptom improvement in both groups and a superior improvement in a subgroup analysis of male patients.<sup>209</sup>

### Conclusion

PPI-refractory GERD is a common problem affecting a large percentage of patients with GERD. Refractory GERD likely does not have a single underlying cause and may actually represent several disease states. Potential causes include medication noncompliance, visceral hypersensitivity, nonacid reflux, motility disorders, and alterations in PPI metabolism. Other disease states such as achalasia, EoE, and esophageal cancer must also be considered. The mainstay of evaluation of a patient with refractory GERD is upper GI endoscopy and impedance monitoring to clarify the nature of any residual reflux. Most therapies involve optimizing GERD treatment and targeting the underlying mechanism of resistance if identified. Therapies range from pharmacologic to procedural to alternative and complementary.

### Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

### Disclosure

The authors report no conflicts of interest in this work.

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