Abstract and Introduction

**Abstract**

**Purpose of review** Patients with gastroesophageal reflux disease (GERD) who are not responding to proton pump inhibitors (PPIs) given once daily are very common. These therapy-resistant patients have become the new face of GERD in clinical practice in the last decade and presently pose a significant therapeutic challenge to the practicing physician. We reviewed newly accumulated information about the management of PPI failure that has been published over the past 2 years.

**Recent findings** There are diverse mechanisms that contribute to the failure of PPI treatment in GERD patients and they are not limited to residual reflux. Some of the causes of PPI failure may coincide in the same patient. Upper endoscopy appears to have limited diagnostic value. In contrast, esophageal impedance with pH testing on therapy appears to provide the most insightful information about the subsequent management of these patients. Commonly, doubling the PPI dose or switching to another PPI will be offered to patients who failed PPI once daily. Failure of such therapeutic strategies is commonly followed by assessment for residual reflux. There is growing information about the potential value of compounds that can reduce transient lower esophageal sphincter relaxations. Esophageal pain modulators are commonly offered to patients with functional heartburn, although supportive clinical studies are still missing.

**Summary** Management of refractory GERD patients remains an important clinical challenge. Recent studies have cemented the value of impedance-pH testing in pursuing proper treatment. Presently, the most promising therapeutic development for this patient population is transient lower esophageal sphincter relaxation reducers.

**Introduction**

It has been estimated that between 10 and 40% of patients with GERD fail to respond symptomatically, either partially or completely, to a standard-dose proton pump inhibitor (PPI).\[1,2\] During a period of only 7 years (1997–2004), there was an increase by almost 50% in the usage of at least double-dose PPI in patients with GERD.\[3\] In a recent US survey of 617 GERD patients taking PPIs, 71% used PPIs once a day, 22.2% twice a day and 6.8% more than twice a day or on as-needed basis.\[4\] Approximately 42.1% of all patients supplemented their prescription PPIs with other antireflux therapies, including over-the-counter antacids and H2-receptor antagonists (H2RAs). Although more than 85% of the patients still experienced GERD-related symptoms, 72.8% claimed to be satisfied or very satisfied with their PPI treatment.

In the 2000 Gallup Study of Consumers’ Use of Stomach Relief Products, 36% reported taking nonprescription medication in addition to a prescription medication for GERD (Fig. 1).\[2\] Of those, 56% stated that they used their prescription medication daily but still needed to supplement with nonprescription medication for breakthrough symptoms. Interestingly, 28% stated that only the combination of prescription and nonprescription medications relieved their symptoms, and 24% reported that the prescription medication worked better in the long run, but the nonprescription medication was faster acting.
Figure 1. Reported type of medications used in the past 30 days in 1009 patients that were surveyed

The box shows the common explanations given by patients with GERD for adding a nonprescription drug to a prescription drug. GERD, gastroesophageal reflux disease. Reproduced from [2].

Failure of PPI treatment to resolve GERD-related symptoms has become the most common presentation of GERD in gastrointestinal practice. Whereas cost analysis of PPI failure has yet to be carried out, it is likely an expensive clinical problem due to repeated utilization of healthcare resources such as clinic visits, diagnostic tests, and prescription medications.

Most of the GERD patients who are not responsive to PPIs are from the nonerosive reflux disease (NERD) and functional heartburn groups, primarily due to the high frequency of these groups in the heartburn patient population (up to 70%) and their known low response rate to PPI once daily.[3,5] In contrast, patients with erosive esophagitis, who account for 30–40% of the total GERD population, have a symptom response rate significantly higher than what has been reported in patients with NERD (pooled symptomatic response rate to PPI once daily at 4 weeks is 56%).[3,6–7]

The Rome III Committee for Functional Esophageal Disorders redefined the functional heartburn group, and consequently NERD, by primarily incorporating the hypersensitive esophagus group and those patients with negative symptom association who are responsive to PPI treatment back into the NERD group (Fig. 2).[7] Presently, functional heartburn is recognized as one of the most important conditions that contributes to PPI failure among patients with heartburn.
Figure 2. A diagnostic algorithm of NERD and functional heartburn based on Rome III criteria
NERD, nonerosive reflux disease.

Definition

What constitutes refractory GERD remains an area of controversy. Most investigators believe that only GERD patients who exhibit partial or lack of response to PPI twice daily should be considered PPI failures, whereas others suggest that lack of satisfactory symptomatic response to PPI once a day is a sufficient criterion for PPI failure. The latter definition is much more relevant to pharmaceutical companies and third-party payers, because there is no GERD-related indication for prescribing PPIs twice a day. Furthermore, it is unclear what symptom burden during PPI consumption fulfills the definition of refractory GERD. This is likely to vary from one individual to another. Because refractory GERD is a patient-driven phenomenon, PPI failure patients who seek medical attention will exhibit different frequency and/or severity of GERD-related symptoms. Consequently, any attempt to narrow the definition of refractory GERD might exclude many true sufferers.

Diagnostic Tests

Management of a patient with 'refractory GERD' requires a high level of certainty about the initial diagnosis of GERD that prompted the PPI therapy. It should be determined if the diagnosis of GERD was based solely on symptoms (subjective findings) or if objective tests, such as upper endoscopy or pH testing, were utilized. A management algorithm for GERD patients who failed PPI once daily is presented in Fig. 3.
Various mechanisms have been shown to contribute to the failure of PPI treatment. At present, much of the research conducted in this area is focused on weakly acidic reflux and esophageal hypersensitivity.\[9\]

Compliance with treatment and proper PPI dosing also are important considerations. Several surveys have demonstrated that poor compliance with PPI treatment is not uncommon among patients with GERD. In a large, population-based study, it was demonstrated that the main factors influencing compliance were the presence or absence of symptoms, the severity of symptoms, and a personal preference about when to take treatment.\[10\] In addition to compliance, timing and frequency of dosing are critical for maximum efficacy of the medication. In a study of 100 patients with persistent GERD symptoms, only 46% dosed optimally the PPIs (i.e. took PPIs within 30 min of a meal).\[11\] Of those who dosed suboptimally, 39% consumed their PPI more than 60 min before meals, 30%...
Recently, weakly acidic and alkaline reflux has been implicated as a cause for refractory GERD-related symptoms. The mechanism by which weakly acidic reflux causes symptoms remains poorly understood. Some authorities have proposed that mechanical distension of the esophagus and/or esophageal hypersensitivity are the culprits. Thus far, there is no evidence that weakly acidic reflux is more commonly associated with increased volume of refluxate than acidic reflux. Although esophageal impedance can document an association between weakly acidic reflux and symptoms, esophageal impedance is unable to measure volume.

Several studies have demonstrated that the proximal extent of weakly acidic reflux (a possible surrogate of volume reflux) was the most important determinant of symptomatic reflux events in patients who failed PPI treatment. However, these studies also demonstrated a considerable overlap in the proximal extent between symptomatic and asymptomatic weakly acidic reflux episodes. In addition, symptomatic reflux episodes in patients who failed PPI twice daily were often composed of both gas and liquid. There are several potential explanations for the association between proximal migration of a reflux event and symptoms. These include increased sensitivity of the proximal esophagus as compared with the distal esophagus and/or 'summation effect' due to greater recruitment of sensitized pain receptors along the esophagus. Recently it was demonstrated that the transition zone between the striated and smooth muscle of the esophagus is more sensitive to mechanical stimulation than the distal esophagus, which has only smooth muscle.

Diagnostic tests in refractory GERD are primarily utilized to identify residual reflux (acidic, nonacidic or bile), anatomical and histological abnormalities of the upper gastrointestinal tract and functional heartburn. The currently available diagnostic techniques for refractory heartburn patients are summarized below:

1. Upper gastrointestinal endoscopy
2. Esophageal biopsies for dilated intercellular spaces (DIS)
3. Ambulatory 24-h esophageal pH monitoring/wireless pH capsule ('Bravo')
4. Ambulatory 24-h esophageal impedance and pH monitoring
5. Esophageal Bilitec

Upper Gastrointestinal Endoscopy

Upper endoscopy is commonly used in clinical practice to evaluate patients with GERD who have failed PPI treatment. This clinical strategy has been endorsed by the American Society of Gastrointestinal Endoscopy (ASGE). The hope is to identify anatomical and histological abnormalities that can explain the treatment failure. However, the benefit of this practice has been challenged by a recent study that evaluated GERD-related endoscopic and histologic findings in patients with refractory GERD (failure to once-daily PPI therapy) vs. patients with heartburn who had not received antireflux treatment. A total of 105 patients (mean age 54.7 years; 71 men, 34 women) were enrolled into the refractory GERD group and 91 (mean age 53.4 years; 68 men, 23 women) into the no-treatment group. Anatomical findings during upper endoscopy were significantly more common in the no-treatment group compared with the refractory GERD group (55.2 vs. 40.7%, P < 0.05). GERD-related findings were significantly more common in the no-treatment group compared with the refractory GERD group (erosive esophagitis: 30.8 vs. 6.7%, respectively, P < 0.05). Refractory GERD was associated with a significantly decreased odds ratio (OR) of erosive esophagitis as compared with no treatment when adjusted for age, sex, and body mass index (BMI) (adjusted OR 0.11, 95% confidence interval (CI) 0.04–0.30). Eosinophilic esophagitis was found in only 0.9% of refractory GERD patients.

In general, the value of endoscopy in discovering GERD-related findings in patients with refractory GERD is very low. This is primarily due to the predominance of NERD and functional heartburn patients among this group of patients and the high efficacy of PPIs in healing erosive esophagitis. Studies have demonstrated that the healing rates of erosive esophagitis in patients receiving standard-dose PPI are high (ranging from 75 to 95%), and endoscopic healing of erosive esophagitis is commonly accompanied by symptom improvement. Persistence of symptoms despite PPI treatment may reflect failure in healing esophageal mucosal injury, almost always in those with more severe grades of erosive esophagitis (C and D). In rare cases, endoscopy in heartburn patients who have failed PPI treatment may reveal a non-GERD-related cause of the symptoms (e.g. eosinophilic esophagitis, ulcers due to Zollinger-Ellison syndrome, pill-induced esophagitis, achalasia, gastroparesis and skin diseases with esophageal involvement).

Esophageal Biopsies and Dilated Intercellular Spaces

Dilated intercellular spaces (DIS) in the esophageal mucosa can be identified in virtually all GERD patients. The presence of DIS is associated with a reduced potential difference, diminished transepithelial resistance, and increased esophageal mucosal...
Other reflux components like bile acids, trypsin, and lipase have also been shown to result in DIS. In addition, experimental exposure of the esophageal mucosa to weakly acidic solutions with or without bile acids (similar to what could happen in refractory GERD patients) can lead to DIS. Interestingly, such perfusions of the distal esophagus can lead to DIS, not only in the ‘exposed’ mucosa, but also in the more proximal, ‘nonexposed’ esophageal mucosa. However, induction of DIS may not coincide with reports of heartburn. Moreover, DIS are not a specific feature of GERD and can be found in up to 30% of asymptomatic patients, as well as in patients with esophageal candidiasis, food allergy, eosinophilic esophagitis, and esophageal cancer.

A recent preliminary study suggests that NERD patients refractory to PPI demonstrate persistence of DIS. In this study, 10 reatatory-NERD patients on PPI twice daily underwent 24-h esophageal impedance and pH monitoring as well as upper endoscopy with biopsies. Measurements of DIS diameter in the failure group on PPIs were compared with those from 33 NERD responders off therapy and 12 asymptomatic volunteers. The mean DIS diameter in both NERD groups was significantly greater, both in the distal and proximal esophagus, than that of the asymptomatic volunteers. Importantly, the DIS diameter in the distal esophagus of the NERD responders off therapy was greater than that of the PPI failure group. No differences in DIS diameter were observed in the proximal esophagus between the two NERD groups. This study suggests that refractory NERD patients demonstrate abnormal DIS diameter throughout the esophagus, although less than that of NERD responders off any antireflux treatment.

Ambulatory 24-h Esophageal pH Monitoring

Both catheter and wireless esophageal pH monitoring allow the quantification of esophageal acid exposure and the assessment of the temporal relationship between symptoms and acid reflux events. Esophageal pH monitoring is commonly used in the evaluation of patients with refractory GERD. In the assessment of such patients, pH monitoring can be performed off PPI to test if the initial diagnosis was correct (i.e. heartburn was due to acid reflux) or on PPI to test whether the symptoms are due to residual acid reflux. Inclusion of a symptom-reflux correlation measure such as symptom index and/or symptom association probability (SAP) helps to determine the relationship between heartburn episodes and acid reflux events, regardless if the pH test is normal or abnormal. Some authorities have suggested that the threshold for abnormal pH test should be lowered in patients undergoing pH testing on PPI therapy. Kuo and Castell proposed a cut-off of 1.6% based on a study in healthy individuals treated with omeprazole 40 mg once daily. However, most gastrointestinal motility laboratories use the classic DeMeester and Johnson criteria (i.e. normal is esophageal pH <4 for <4.2% of the monitoring period) irrespective of PPI treatment.

A positive pH test on PPI suggests that patients' persistent heartburn might be related to ongoing acid reflux. If the pH test is normal on PPI treatment, but the symptom index is abnormal, then heartburn induced by physiological levels of acid exposure could be the explanation. A normal pH test on PPI with a negative symptom index suggests that the patient's heartburn is unlikely to be related to ongoing acid reflux. However, a negative pH test may result from the patient's poor tolerance of the pH probe that causes them to limit reflux-provoking activities.

Residual acid reflux has been documented in GERD patients with persistent heartburn despite treatment with PPI once or twice daily. In one study, 38.6% of the GERD patients undergoing pH testing for persistent symptoms while on PPI once a day were found to have an abnormal pH test. There was no correlation between a negative pH test and age, sex, or brand of PPI. In another study, 31 and 4% of the GERD patients with refractory symptoms on PPI once daily and PPI twice daily, respectively, had an abnormal pH test. Recently, Karamanolis et al. demonstrated that 16 and 32% of the symptomatic patients on double dose and standard dose PPI, respectively, had an abnormal pH test. Overall, positive symptom index was documented in 40% and 7–11% of the patients who remained symptomatic on PPI once or twice daily, respectively.

Extending the usage of the wireless pH monitoring to 4 days has been suggested to provide a better comparison of esophageal acid exposure and symptom reflux association between off and on PPI treatment periods. However, studies evaluating this diagnostic strategy in refractory GERD patients are still missing.

Nocturnal acid breakthrough (NAB), defined as gastric pH below 4 for at least 1 h during the night, has been observed in 75% of all individuals (GERD patients as well as healthy individuals) taking a PPI twice daily. It has been proposed that NAB might be a
cause of PPI-refractory GERD. However, studies have shown that NAB does not exhibit a temporal relationship with reflux-related symptoms. In one study, 71% of patients with GERD who did not respond to twice-daily PPI experienced NAB, but only 36% showed a correlation between symptoms and NAB.[43] Furthermore, no relationship between NAB and nocturnal heartburn has ever been established.

**Esophageal Multichannel Intraluminal Impedance-pH Monitoring**

Multichannel intraluminal impedance-pH (MII-pH) monitoring allows the detection of virtually all reflux events and the distinction between acidic, weakly acidic, and weakly alkaline reflux.[44] Studies using this technique have suggested that persistent typical as well as atypical GERD symptoms in patients taking PPIs might be due to nonacidic reflux (weakly acid or alkaline).

The first stationary, postprandial impedance-pH study in patients who failed PPI twice daily documented a shift from primarily acidic reflux at baseline before PPIs to mostly weakly acidic reflux during PPI therapy. Furthermore, regurgitation became the predominant symptom in patients who failed PPI twice daily.[45] Further studies using ambulatory MII-pH monitoring in patients who failed PPI twice daily demonstrated that acidic reflux was associated with 7–28% of the persistent GERD symptoms, whereas weakly acidic reflux preceded 30–40% of the symptoms. Between 30 and 60% of symptoms were not preceded by any reflux.[39,46,47]

A recent MII-pH study in refractory GERD patients on PPI therapy showed that up to 68% of heartburn episodes were associated with weakly acidic reflux.[13] High esophageal proximal extent was the only important factor associated with reflux perception. Furthermore, as compared with regurgitation, weakly acidic reflux episodes resulting in heartburn were more frequently pure liquid, slightly more acidic with a lower nadir pH (4.8 vs. 5.5), and were more commonly associated with preceding acid reflux episodes.

An important controversy in patients with refractory GERD is whether to conduct testing on or off PPI therapy. Zerbib et al.[47] reported the results of MII-pH monitoring in a group of patients off vs. those on twice a day PPI treatment. In patients off PPI, combined MII-pH monitoring added little to pH monitoring alone (5–10%). In patients on PPI therapy, however, adding impedance to pH monitoring improved the diagnostic yield by 15–20%, with better symptom correlation analysis than that during pH testing alone.[47]

Another recent study compared the results of MII-pH monitoring in 39 patients with refractory GERD on twice-a-day PPI therapy with those of wireless pH monitoring in the same patients off PPI therapy.[48] On PPI therapy, all patients had normal esophageal acid exposure, and 64% had normal impedance parameters for weakly acidic and alkaline reflux, suggesting that causes other than GERD were responsible for symptoms. Of the patients with abnormal MII-pH results on therapy, 93% also had abnormal esophageal acid exposure when studied by wireless pH monitoring off therapy. Furthermore, patients with abnormal weakly acidic or alkaline reflux by MII-pH were significantly more likely to have a greater degree of abnormal esophageal acid exposure at baseline than patients with normal impedance results. The study suggests that abnormal MII-pH on twice-daily PPI predicts abnormal esophageal acid exposure at baseline, and functional heartburn is unlikely in those patients.

Another recent study compared the yield of MII-pH monitoring on twice-daily PPI vs. off-treatment PPI in refractory heartburn patients. In contrast to the aforementioned studies, the investigators found that off-treatment PPI MII-pH testing provided a higher diagnostic yield than on-treatment PPI MII-pH testing for refractory GERD.[49] The main limitations of this study are the focus on SAP and the cessation of PPI treatment for only 7 days prior to MII-pH testing.

**Esophageal Bilitec**

Esophageal Bilitec monitoring detects refluxed bilirubin, which is a surrogate marker for bile reflux. One should note that nonacidic reflux and bile reflux are distinct phenomena. A recent study evaluated 20 patients with refractory GERD with both Bilitec and MII-pH monitoring.[50] The authors demonstrated abnormal duodeno-gastroesophageal reflux (DGER) in nine cases, and six of those had normal values for nonacidic reflux. Also, there was no correlation between the two types of reflux.

There is evidence that esophageal exposure to bile acids can cause heartburn. For example, esophageal perfusion with bile salt solutions at nonacidic pH has been shown to provoke heartburn.[51] In addition, exposure of rabbit esophageal mucosa to weakly acidic solutions containing bile acids resulted in increased mucosal permeability and induced DIS.[52]

Tack et al.[53] suggested a possible role for DGER in a subset of patients with difficult to manage, symptomatic reflux. In a study that included 65 patients with persistent heartburn and regurgitation while on single or double-dose PPI therapy, the authors demonstrated that 64% of the patients experienced symptoms that were associated with bile reflux alone or in combination with acid. The role of adding Bilitec to conventional pH monitoring was also assessed in 347 patients (157 men, mean age 49.4 years) who underwent pH studies on PPI therapy (28% half-dose, 67% single-dose, and 5% double-dose PPI) for persistent typical (53%) or

atypical (75%) GERD symptoms.\textsuperscript{[37]} The addition of Bilitec increased the number of abnormal results over pH monitoring alone, from 38 to 69% on half-dose, from 27 to 69% on single-dose, and from 0 to 38% on double-dose PPI.

Most studies evaluating patients with refractory GERD tend to compare reflux patterns at baseline and during PPI treatment. However, these studies do not provide the answer to the 'burning' query if residual reflux (acidic, nonacidic or bile) is a unique PPI failure phenomenon or a general phenomenon that occurs in all patients on PPIs, irrespective of their symptomatic response. To answer this question, the reflux pattern of responders and nonresponders to the same dose of PPI should be compared. Recently, a study evaluated 24 patients who failed and 23 patients who fully responded to a PPI once a day using both 24-h esophageal Bilitec and pH monitoring during treatment.\textsuperscript{[54•]} The authors demonstrated that abnormal DGER occurred in 82% of the responders vs. 67% of the nonresponders ($P = \text{n.s.}$). Indeed, all pH testing and Bilitec parameters were similar between the two groups. However, GERD symptoms in the PPI-failure group were more commonly associated with acid reflux than with DGER. This study demonstrated for the first time that the level of bile and acid exposure is similar among patients who fail and those who respond to treatment with a PPI once daily. In addition, in patients who failed to respond to PPI once daily, acidic reflux still appears to play an important role in symptom generation. Finally, although PPI therapy reduces both acid and bile reflux,\textsuperscript{[55,56]} complete acid suppression does not guarantee elimination of DGER.\textsuperscript{[57,58]}

**Treatment**

Evaluation for proper compliance and optimal dosing time should be the first management step in assessing patients with heartburn not responding to PPI therapy.\textsuperscript{[59]} The physician should emphasize the need to take PPIs half an hour before a meal.

**Lifestyle Modifications**

The benefit of lifestyle modifications in GERD patients who fail PPI treatment has yet to be elucidated. In a recent systematic review of reports on lifestyle modifications for GERD, the authors determined that only weight loss and elevation of head of the bed appear to be effective.\textsuperscript{[60]} There were insufficient data to support any of the other commonly prescribed lifestyle modifications. Nevertheless, in patients with PPI-refractory heartburn, it seems reasonable to recommend avoidance of specific lifestyle activities that appear to trigger GERD symptoms.

**Histamine 2 Receptor Antagonists**

For GERD patients on PPI twice daily who exhibit NAB, early studies showed that the addition of a histamine 2 receptor antagonist (H2RA) at bedtime significantly reduced the frequency and duration of NAB.\textsuperscript{[61]} Although no studies document any clinical correlation between NAB and nocturnal GERD symptoms, the addition of H2RA at bedtime has become common practice in GERD patients who fail PPI treatment. However, patients rapidly develop tolerance (within 1 week) to the antisecretory effects of H2RAs given at bedtime.\textsuperscript{[62]}

In a study that evaluated 100 patients (58 on twice-daily PPI and 42 on twice-daily PPI + H2RA at bedtime for at least 1 month), the authors demonstrated that the addition of a bedtime H2RA significantly reduced the percentage time with intragastric pH below 4 during upright, recumbent, and the entire monitoring period.\textsuperscript{[63]} Unfortunately, the authors failed to provide any evidence for clinical effects of the bedtime H2RA. Rackoff et al.\textsuperscript{[64]} evaluated 56 GERD patients on PPI twice daily who were receiving H2RA at bedtime for variable durations. The authors found that 72% of patients reported improvement in overall symptoms, 74% in night-time reflux symptoms, and 67% in GERD-associated sleep disturbances.

**Proton Pump Inhibitors**

Currently, PPIs are the most efficacious treatment for both healing erosive esophagitis and for symptom relief in GERD patients. In those who fail PPI once a day, there are two major potential therapeutic strategies that are utilized in clinical practice – switching to another PPI or doubling the dose of the same PPI. Doubling the PPI dose is by far the most common therapeutic strategy used by practicing physicians, and this strategy is recommended by the 2008 American Gastroenterological Association guidelines for GERD.\textsuperscript{[65]} The Cochrane review suggests that doubling the PPI dose is associated with greater healing of erosive esophagitis, with a number-needed-to-treat (NNT) of 25. However, there is no clear PPI dose–response relationship for heartburn resolution in either erosive esophagitis or NERD.\textsuperscript{[66]}

Switching to another PPI is an attractive therapeutic strategy that could be utilized in the management of patients who failed PPI once daily. In one study, patients who failed lansoprazole 30 mg once daily were randomized to either double-dose lansoprazole or 40 mg once-daily esomeprazole. Single-dose esomeprazole was as effective as double-dose lansoprazole in percentage of heartburn-free days as well as symptom score for heartburn, acid regurgitation, and epigastric pain.\textsuperscript{[67]}


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Whereas doubling the PPI dose might be considered the standard of care, there is no evidence to support any further escalation of the PPI dose for symptom control or healing of erosive esophagitis. For double-dose therapy, the PPI should be taken before breakfast and before dinner. Support for this regimen comes primarily from studies demonstrating improved control of intragastric pH when one PPI pill is taken before breakfast and dinner rather than taking two pills before breakfast.\(^{68}\)

A recent study has suggested that a minority of GERD patients may lose PPI efficacy after 2 years of continuous and unmodified treatment with one or two PPIs per day.\(^{69}\) The sole parameter evaluated in this study was the level of esophageal acid exposure as assessed by pH testing. The authors did not provide any clinical data to correlate with their physiological findings. In another study, the authors demonstrated that infection with *Helicobacter pylori* in healthy individuals, who are CYP2C19 extensive metabolizers, eliminated the differences in intragastric pH control between standard and double-dose PPI.\(^{70}\) As with the previous study, the authors did not provide any clinical endpoints to correlate with the pH monitoring data.

The value of utilizing dexlansoprazole MR, an R-enantiomer of lansoprazole that also has dual delayed release (DDR) technology in patients who failed standard-dose PPI, remains to be elucidated.\(^{71,72}\) Conceivably, the dual release of the drug (separated by 4–5 h), might be helpful in patients who failed PPI once daily.

### Transient Lower Esophageal Sphincter Relaxation Reducers

A number of receptors have been shown to be involved in triggering transient lower esophageal sphincter relaxation (TLESR) providing the opportunity to develop novel reflux inhibitors.\(^{73}\) The most promising of these agents appear to be the gamma-aminobutyric acid B (GABAB) receptor agonists and metabotropic glutamate receptor 5 (mGluR5) antagonists, which can achieve a high level of TLESR inhibition.\(^{73,74}\)

Baclofen, a GABAB agonist, is a potential add-on treatment for patients who failed PPI therapy.\(^{75,76}\) The drug reduces the TLESR rate by 40–60\%, reduces reflux episodes by 43\%, increases lower esophageal sphincter basal pressure, and accelerates gastric emptying.\(^{75–77}\) Baclofen has been shown to significantly reduce DGER and weakly acidic reflux as well as DGER-related symptoms.\(^{58,78}\) In patients with persistent heartburn despite PPIs, baclofen doses of up to 20 mg three times daily have been used.\(^{68}\) Because the drug crosses the blood–brain barrier, a variety of central nervous system (CNS)-related side effects have been reported including somnolence, confusion, dizziness, lightheadedness, drowsiness, weakness, and trembling. The side effects are likely an important limiting factor in the routine usage of baclofen in clinical practice.

Arbaclofen placarbil (also known as XP19986) is a novel, transported pro-drug of the pharmacologically active R-isomer of baclofen. The drug is currently in clinical development for the treatment of refractory GERD. Arbaclofen placarbil was designed to be efficiently absorbed in the gastrointestinal tract and rapidly metabolized to release R-baclofen after absorption. Unlike baclofen, arbaclofen placarbil is well absorbed from the colon, allowing the drug to be delivered in a sustained release formulation that may allow less frequent dosing and thus reduced fluctuations in plasma exposure. This in turn may lead to potentially improved efficacy through a combination of greater duration of action, dosing convenience, and better safety profile compared with baclofen.\(^{79,80}\)

The effect of ADX10059, a potent, selective, negative allosteric modulator (NAM) of mGluR5, on esophageal acid exposure and symptoms has been recently evaluated in GERD patients. ADX10059 at a dose of 250 mg three times daily was well tolerated, and significantly reduced both the percentage of time esophageal pH below 4 and the duration of symptomatic reflux episodes.\(^{81}\) However, on 14 December 2009 Addex Pharmaceuticals Ltd. ended development of ADX10059 because of a possible link to severe hepatic side effects.

### Visceral Pain Modulators

To date, there are no studies that have specifically evaluated visceral pain modulators in refractory GERD patients. However, given the fact that most patients who fail PPI treatment have NERD and most do not have abnormal acid reflux when they are taking PPIs, the use of pain modulators is highly attractive.\(^{39,82}\) Pain modulators such as tricyclic antidepressants, trazodone (a tetracyclic antidepressants), and selective serotonin reuptake inhibitors (SSRIs) have all been shown to improve esophageal pain in patients with noncardiac chest pain.\(^{59,83,84}\) It is believed that these agents confer their visceral analgesic effect by acting at the CNS and/or peripherally at the sensory afferent level.

For visceral pain syndromes, the pain modulators are used in doses lower than those given for mood alteration. Nevertheless, side effects are common, and may limit the usage of pain modulators in certain patient populations, like the elderly or those with multiple comorbidities.
**Botulinum Toxin Injection**

In one recent study, botulinum toxin was administered by pyloric injection to 11 patients who had refractory GERD associated with gastroparesis. There was marked improvement in GERD-related symptoms, which correlated with improvements in gastroparesis-related symptoms and in gastric-emptying as assessed by scintigraphy. The mean duration of response is approximately 5 months.

**Antireflux Surgery**

A recent surgical study reported that refractory GERD was the most common (88%) indication for antireflux surgery. Interestingly, the most common preoperative symptom reported under failure of medical antireflux treatment was regurgitation (54%). Overall, 82% of patients reported that the preoperative reflux symptom completely resolved, and 94% were satisfied with the results of the surgery. In another study that included only 30 patients with refractory GERD who were followed for a period of 12 months, the main preoperative symptoms were regurgitation (93%) and heartburn (60%). At the end of 1 year follow-up after surgery, all patients reported complete heartburn relief and 86% reported resolution of the regurgitation symptom. Patients' satisfaction rate with surgery was 87%.

Three recent studies have suggested that a positive symptom index during impedance-pH monitoring in patients with PPI-refractory GERD (on therapy) can predict a favorable response to medical or surgical therapy. The first study by Mainie et al. followed 19 patients who were refractory to double-dose PPI and underwent a successful laparoscopic Nissen fundoplication. Prior to surgery, 18 of the 19 patients were found to have a positive symptom index on MII-pH monitoring (14 with nonacid and 4 with acid reflux). After a mean follow-up of 14 months, 16 of the patients with a positive symptom index were asymptomatic. The second study by Becker et al. assessed 56 patients with persistent symptoms on a single dose of PPI and abnormal MII-pH monitoring. Most of these patients had a positive symptom index, and later demonstrated a significantly higher response rate to doubling the PPI dose compared to patients with normal MII-pH monitoring results. In a third study, a group of Italian investigators prospectively assessed the outcomes of laparoscopic Nissen fundoplication in 62 patients who were PPI-nonresponsive or noncompliant. All surgically treated patients had a positive MII-pH monitoring result. The overall patient satisfaction rate was 98.3%, and no differences were found in clinical outcomes based on preoperative MII-pH or manometry results. It was concluded that MII-pH provide useful information for better selection of patients for antireflux surgery and that laparoscopic Nissen fundoplication results in excellent outcomes primarily in patients with positive MII-pH monitoring or symptom index. Unfortunately, all the aforementioned studies were uncontrolled and did not clearly describe whether symptoms were due to residual reflux.

**Alternative Medicine**

The value of acupuncture has been evaluated in GERD patients who failed PPI once daily. When compared to doubling the PPI dose, adding acupuncture was significantly better in controlling regurgitation as well as daytime and night-time heartburn. This is the first study to suggest that alternative approaches for treating visceral pain may have a role in GERD patients with PPI-refractory heartburn.

**Psychological Treatment**

Patients with poor correlation of symptoms and acid reflux events display a higher level of anxiety and hysteria than those who have a close correlation between symptoms and acid-reflux. Anxiety and depression have been shown to increase GERD-related symptoms report in population-based studies. Nojkov et al. provided the first evidence that response to PPI treatment may be dependent on the level of psychological distress. Thus, it has been proposed that patients who do not respond to PPIs are more likely to have a psychological comorbidity than those who respond. In those patients, treatment directed toward the underlying psychosocial abnormality might improve the response to PPI therapy.

**Future Therapy**

Several directions in drug development have been pursued in patients who failed PPI treatment. These include more early and profound acid suppression, reduction in the rate of TLESRs, improving esophageal and/or gastric motility, attenuation of esophageal pain and mucosal coating of the esophagus.

Vecam, a combination of a PPI and succinic acid (an acid pump activator, VB101), is a drug that has meal-independent antisecretory effect. Oral administration of succinic acid in humans has the same acid-stimulating activity as pentagastrin, and succinic acid given to rats augments PPI antisecretory effects.
AGN 201904-Z is a slowly absorbed, acid-stable pro-PPI that rapidly converts to omeprazole in the systemic circulation. A single oral dose provides continued metered absorption (CMA) that prolongs plasma residence time. Consequently, the activated proton pumps are exposed over longer period of time to the drug. In a 5-day phase I study, AGN 201904-Z produced a significantly greater acid suppression than esomeprazole 40 mg per day. Nocturnal acid suppression also was significantly greater for AGN 201904-Z, which reduced the proportion of patients exhibiting NAB (25 vs. 100%).[95]

Tenatoprazole is an imidazopyridine-based PPI with a prolonged plasma half-life. Tenatoprazole 40 mg daily provides better nighttime acid control than esomeprazole 40 mg once daily. In a single-center, double-blind, double-dummy, randomized, four-way crossover study that was conducted in 32 healthy male individuals, S-tenatoprazole-sodium produced significantly more prolonged 24-h and nocturnal acid suppression than esomeprazole 40 mg.[96]

Several new compounds that combine a PPI with an H2RA have been recently evaluated. All are still in early stages of development. The fast-dissolving OX 17 is a fixed-dose combination of omeprazole and famotidine. This drug has undergone several phase II/III clinical trials.[97] In addition, a combination of an H2RA with tenatoprazole has been recently patented.[98] Further studies are needed to determine the value of these compounds in refractory GERD patients.

Conclusion

As previously mentioned, the main focus for drug development in refractory GERD patients is TLESR reduction and more potent, early and consistent acid suppression. However, due to the diverse causes of PPI failure, one therapeutic strategy may not be the solution for all patients. It is likely that individually tailored therapy will be the best management approach.

References

1. Inadomi JM, McIntyre L, Bernard L, et al. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. Am J Gastroenterol 2003; 98:1940–1944.


• This study cements the values of impedance pH as a predictive tool for true GERD patients.


• The first study that compares acidic and DGER pattern between responders and nonresponders to PPI treatment.


Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 412–414).