INTRODUCTION

Acid suppression with proton pump inhibitors (PPIs) is the mainstay of therapy for gastrooesophageal reflux disease (GORD). It is known that resolution of oesophageal mucosal inflammation is more likely to occur than resolution of symptoms. It has been estimated that between 10% and 40% of the patients with GORD fail to respond symptomatically, either partially or completely, to a standard dose PPI.1,2,3 Failure of the PPI treatment to resolve reflux symptoms has become one of the most common presentations of GORD in gastro-intestinal (GI) clinical practice. As GORD is one of the most prevalent chronic disorders in the Western world, even a small proportion of GORD patients becoming therapy-resistant encompasses a substantial part of the work load of general practitioners, internists and gastroenterologists.

Most of the patients with reflux symptoms who are not responsive to PPIs originate from the non-erosive reflux disease (NERD) phenotype (box 1), primarily due to their relative large size in the GORD patient population (up to 70%) and low response rate to PPI once daily (response pooled rate 36%).4,5 In addition, it appears that NERD patients with normal or only mildly abnormal oesophageal acid exposure, who account for a significant portion of the NERD group, exhibit a relatively lower symptom response rate to PPI once daily as compared with the other patients with NERD. Functional heartburn (box 1) patients with normal endoscopy and normal pH testing exhibit the lowest symptom response rate to PPI.

Patients with GORD often have functional digestive disorders that may also influence the response to therapy. The association of heartburn with dyspeptic symptoms including epigastric pain, bloating, early satiety and nausea/vomiting is present in approximately a third of GORD patients. Dyspeptic symptoms contribute significantly to the decrement in health-related quality of life related to GORD and are less likely to respond to antireflux therapy.6

GORD is a costly disease, resulting in consultation, referral and treatment costs of nearly $10 billion annually in the USA7 and PPI failure represents an expensive clinical problem due to repeated utilisation of healthcare resources such as clinic visits, diagnostic tests and prescription medications.8 It can also be a significant financial burden on society through the cost of long-term reduced work productivity and increased work absenteeism.9

The abovementioned prevalence and relevance of PPI-refractory reflux symptoms outline the need for new treatment options for symptomatic patients taking PPI therapy.

This review will first examine and update the definition, potential pathophysiological mechanisms, clinical evaluation and current or developing therapeutic options for patients with reflux symptoms incompletely responsive to PPI therapy; in a second part, an algorithm for management and treatment will be proposed.

DEFINITION OF REFRACTORY REFLUX SYMPTOMS

Poor response to PPI is usually defined as <50% improvement in the chief complaint after at least 12 weeks of PPI therapy. The symptom burden must be to a degree that impairs quality of life, and symptoms must be ‘reflux-related’. This distinction in clinical practice can be difficult because of our imperfect tools for establishing whether or not symptoms are attributable to reflux, be it acid reflux, non-acid reflux or gas reflux. What are judged reflux symptoms’ do not necessarily imply that these are due to GORD, as they may also occur in conditions such as functional heartburn and functional dyspepsia. The patient’s perception of remaining symptoms is subjective and dependent on the patient’s expectations of the therapy.10 They are likely to be influenced by sex, age,
**Box 1 Glossary**

- **Refractory reflux symptoms**: symptoms (heartburn and/or regurgitation) not responding to a double dose of a proton pump inhibitor (PPI) during a treatment period of at least 12 weeks.
- **Non-erosive reflux disease**: patients without any mucosal break at endoscopy and abnormal oesophageal acid exposure at 24-h oesophageal pH monitoring.
- **Acid hypersensitive oesophagus**: patients without any mucosal break at endoscopy, normal oesophageal acid exposure and positive symptom-reflux association analysis (SI >50%, SAP >95%).
- **Functional heartburn**: patients with heartburn refractory to PPIs, without any mucosal break at endoscopy, normal oesophageal acid exposure and negative symptom—reflux association analysis (symptom index <50%, symptom association probability <95%) at 24-h oesophageal pH monitoring.

ethnicity, social status, comorbidity and cultural background.11

The PPI regime considered to define refractoriness to treatment is controversial. Some investigators believe that lack of symptomatic response to PPI once a day is sufficient to consider patients as PPI failures. This definition is relevant to pharmaceutical companies and third-party payers and the US Food and Drug Administration-approved dosing of PPI does not extend to twice daily therapy.12

Physicians often double the PPI dose, assuming that a higher PPI dose will eventually result in symptom resolution. However, this therapeutic strategy frequently results in a less than satisfactory symptomatic response and the majority of patients (75%) continue to experience reflux symptoms despite increased doses of PPI.13

Therefore, most investigators suggest that only patients who exhibit incomplete or lack of response to PPI twice daily should be considered as PPI failures.

We propose to use the term PPI-refractory reflux symptoms for the condition in which symptoms (heartburn and/or regurgitation) are not responding to a stable double dose of a PPI during a treatment period of at least 12 weeks and patients continue to report troublesome symptoms while ‘on’ PPI at least 3 times a week for the last 3 months.

**MECHANISMS OF REFRACTORINESS TO PPI**

Refractoriness to PPI can be non-reflux or reflux-related.14 The non-reflux-related oesophageal causes include severe dysmotility syndromes such as achalasia or scleroderma, eosinophilic oesophagitis, pill oesophagitis and infectious oesophagitis. In the absence of structural, motility or inflammatory causes, functional heartburn or functional chest pain should be considered.

The reflux-related causes can be: (a) persistent acid reflux, due to incorrect medication dose timing, medication non-compliance, pathological acid secretion, rapid PPI metabolism, a hyper-secretory state, a significant anatomic abnormality like a large hiatal hernia, (b) persistent reflux of non-acid material from either the stomach or the duodenum, (c) persistent impairment of oesophageal mucosal integrity and (d) hypersensitivity to physiological amount of acid, weakly acidic and or gas reflux.

**Residual acid reflux**

Residual acid reflux has been documented in patients with persistent heartburn despite PPIs once or twice daily. In one study, 58.6% of patients undergoing pH testing for persistent symptoms, while receiving standard dose PPIs once a day, had an abnormal test.15 In another study, 31% and 4% of subjects with refractory symptoms had an abnormal pH testing ‘on’ PPIs once daily and twice daily, respectively.16 More recently, Karamanolis et al demonstrated that 16% and 32% of the symptomatic subjects on double dose and standard dose PPIs, respectively, had abnormal pH tests.17 Positive symptom index (SI) with an acid reflux event was noted in 40% and 7%–11% of patients who remained symptomatic ‘on’ PPIs once18 and twice daily,19 respectively. The role of residual acid reflux in the pathogenesis of PPI failure remains controversial. Gasirowska et al reported that the amount of residual acid reflux was not different in responders to PPI and non-responders.11

There are several mechanisms to explain elevated oesophageal acid exposures despite PPI therapy. Once non-compliance has been ruled out, ineffective control of acid secretion may be related to PPI metabolism. A ‘rapid’ PPI metaboliser might not achieve high enough serum levels for adequate acid suppression22 but this is likely a small proportion of treatment failures. Nocturnal acid breakthrough (NAB) has been defined as the presence of gastric pH below 4 for at least 1 h during the night.23 It has been suggested that this gastric physiological phenomenon causes failure of PPI treatment by promoting gastro-oesophageal reflux (GOR) during sleep but several studies have shown that NAB events do not necessarily denote a temporal relationship with reflux-related symptoms;24 Thus far, accumulating data do not support a significant role for NAB in precipitating the failure of PPI treatment.

Finally, if small bowel ulceration accompanies refractory reflux and diarrhoea, a hypersecretory state such as Zollinger–Ellison syndrome could be considered. However, this remains an uncommon cause of refractory reflux.14

**Weakly acidic reflux**

Studies have suggested that persistent typical and atypical reflux symptoms ‘on’ PPIs might be due to less acidic or non-acidic reflux. The first stationary, postprandial impedance-pH study in patients ‘on’ PPI twice-daily therapy documented a profound decrease in the amount of acid reflux but with continuing postprandial reflux of weakly acidic nature. Heartburn was replaced by regurgitation, which became the predominant symptom in these patients.25

The mechanism by which weakly acidic reflux causes symptoms is not completely elucidated.
Recent advances in clinical practice

Three possible explanations can be proposed: oesophageal distension by increased reflux volume, hypersensitivity to weakly acidic refluxate and impairment of oesophageal mucosa integrity after repeated exposure to weakly acidic refluxates. Thus far, there is no evidence that weakly acidic reflux is more commonly associated with increased volume of the refluxate than acidic reflux. Several studies have demonstrated that proximal extent of weakly acidic reflux (a possible indirect marker of reflux volume) was the most important determinant of symptomatic reflux events in patients who failed PPI treatment. However, these studies also showed a considerable overlap in the proximal extent of symptomatic and asymptomatic weakly acidic reflux episodes. Consequently, it is impossible to determine individual thresholds for the point at which weakly acidic reflux episodes consistently provoke symptoms.

Tutuian et al have shown that, in addition to proximal extent, reflux episodes that were associated with symptoms in patients who failed PPI twice daily were primarily composed of both gas and liquid. Proximal migration of gas containing reflux may be more likely to elicit symptoms because the transition zone between the striated and smooth muscle in the oesophagus is more sensitive to mechanical stimulus than the distal oesophagus. A study by Emerenziani et al showed that in heartburn patients with normal endoscopy and pH testing, the risk of reflux perception was significantly higher when gas was present in the refluxate. pH-impedance studies showed that patients with positive association between weakly acidic reflux and symptoms had no significant increased number of this type of refluxate. These studies suggest that if the frequency of weakly acidic reflux is similar between PPI success and PPI failure patients, then PPI failure in these patients might be due to an oesophageal hypersensitivity phenomenon to weakly acidic reflux.

Finally, exposure of the distal oesophagus to weakly acidic solutions with a pH similar to that of gastric refluxate provokes changes in oesophageal mucosal integrity (dilated intercellular spaces or DIS) that can theoretically contribute to persistent symptoms in these patients.

Duodeno-gastro-oesophageal (bile) reflux

Although commonly considered as a synonym, bile reflux and non-acid reflux are completely different phenomena. Previous studies suggested that bile reflux probably accounts for only 10%–15% of non-acid reflux. A study using simultaneous Bilitec and impedance monitoring showed no correlation between the per cent time of bilirubin absorbance and non-acid reflux parameters. The majority of bile reflux occurs concomitantly with acid reflux events, and it is believed that acid rather than bile is the dominant factor responsible for reflux symptoms. Experimental data, however, support a role for persistent bile acids in the refluxate as a potential factor involved in refractory heartburn. Although PPI therapy reduces the occurrence of both acid as well as bile reflux, it has been shown that complete acid suppression does not guarantee elimination of duodeno-gastro-oesophageal reflux (DGOR). Perfusion of bile salts with non-acidic pH can still provoke heartburn and exposure of rabbit oesophageal mucosa to weakly acidic solutions containing bile acids (comparable situation with patients ‘on’ PPIs) increases mucosal permeability and induces DIS, a proposed histopathological mechanism necessary for the sensation of heartburn. In a carefully selected group of patients with symptoms refractory to PPI therapy, baclofen 20 mg three times daily significantly reduced the DGOR exposure as well as symptoms of heartburn. A study by Tack et al suggested a possible role for DGOR in patients with refractory reflux symptoms, but when symptom association was analysed, a positive SI for acid reflux, DGOR, and mixed reflux was found in 19%, 8% and 5% of the patients, respectively. In another study, abnormal DGOR was documented in 82% of the responders versus 67% of the non-responders to PPI once daily. However, only 9% of symptoms were correlated to DGOR suggesting that DGOR plays a limited role in symptom elicitation in refractory GORD patients.

Persistent impairment of oesophageal mucosal integrity

Compared with healthy subjects, the oesophageal mucosal epithelium in NERD patients shows DIS under light and electron microscopy. The presence of DIS in NERD patients is currently considered critical for symptoms perception. Successful symptomatic treatment of NERD with PPIs is almost always associated with DIS resolution, and persistence of symptoms despite PPI therapy has been shown to be associated with the persistence of DIS. Therefore, such chronic changes may allow permeation of noxious or sensitising substances into the intercellular spaces of oesophageal mucosa and may increase nociceptor activation.

Patients with persistent symptoms ‘on’ PPI continue to have pH 5–6 reflux episodes containing bile acids. Experiments in rabbits and humans show that oesophageal mucosal integrity can be altered when exposed to acid and to weakly acid solutions containing bile acids. Such chronic changes may allow permeation of noxious or sensitising substances into the intercellular spaces of oesophageal mucosa and may increase nociceptor activation.

Oesophageal hypersensitivity

Patients with persistent symptoms of reflux and normal upper endoscopies may have normal oesophageal acid exposures but a strong correlation between physiological acid reflux events and symptoms. Visceral hypersensitivity is proposed as the underlying mechanism. It is not known whether patients with reflux symptoms refractory to PPI have more severe...
visceral hypersensitivity that those who respond to therapy. Experimental data indicate that patients with NERD and functional heartburn are more sensitive to intraeosophageal acid challenge, balloon distension or electrical stimulation than patients with erosive disease or controls.47 48 The mechanism of oesophageal hypersensitivity is unclear but involves (among other potential mechanisms) DIS and exposure of subepithelial nerves to acid.49 This leads to sensitisation of peripheral afferent nerves (peripheral sensitisation) and also sensitisation of spinal dorsal horn neurons (central sensitisation).50 Once central sensitisation is established, it can continue to potentiate pain after the initiating peripheral stimulus is discontinued.

During tissue injury and inflammation, a mixture of immune and inflammatory mediators can act on peripheral nociceptor terminals and alter synaptic function by modifying either the release of neurotransmitters from presynaptic terminals or transmitter responsiveness on the postsynaptic membrane. This inflammatory mediator-induced reduction in the transduction threshold of nociceptor primary afferents is believed to cause pain hypersensitivity at the site of injury or inflammation, resulting in a heightened awareness of subsequent painful stimuli (primary hyperalgesia) and the perception of innocuous stimuli as being painful. It is evident that ulceration/erosion of the epithelium as occurs in erosive oesophagitis could expose these endings to H\(^+\) ions directly but this is not the case in NERD. It is likely that low grade inflammation probably plays a role in ‘transducing’ the acid signal in NERD or that DIS, known to be present in NERD, permits some acid penetration. Furthermore, an upregulation of acid-sensitive receptors has been demonstrated in GORD. Recent studies have demonstrated that the transient receptor potential vanilloid 1 (TRPV-1), a non-selective cation channel expressed by epithelial cells and sensory nerves, is present in healthy oesophageal mucosa but upregulated in patients with erosive oesophagitis and NERD.51 In patients with NERD, increased areas of visceral (upper oesophagus or stomach) and somatic hyperalgesia (chest wall) have been demonstrated,52 suggesting that central sensitisation plays an important role.

Functional heartburn is one of the most common causes for failure of PPI treatment. The underlying mechanisms for symptoms in functional heartburn patients remain to be elucidated. Thus far, studies demonstrated increased oesophageal sensitivity to chemical, mechanical and electrical stimuli in this patient population.52–54

**Psychological comorbidity**

Patients with poor correlation of symptoms with acid reflux events display a high level of anxiety and hysteria as compared with patients who demonstrate a close correlation between symptoms and acid-reflux event. Anxiety and depression have been shown to increase reflux symptoms reported in population-based studies. Thus, it has been proposed that patients who did not respond to PPI treatment are more likely to have psychosocial comorbidity than those who were successfully treated with PPIs. A study by Nojkov et al demonstrated that patients who responded less well to PPI treatment were more likely to experience psychological distress.55

Patients with GORD usually report that their heartburn is either triggered by or worsened during lifetime stress events. Psychological stress can exacerbate oesophageal pain hypersensitivity by enhancing both peripheral and central mechanisms. It is known that psychological stress is associated with increased perception of oesophageal stimuli.56 The mechanisms underlying the role of stress in oesophageal hypersensitivity are under current intense investigation. It is tempting to accept that such an effect is mainly produced at the CNS level. Stress alters brain processing of sensation (as demonstrated by functional MRI studies) or by altering the descending inhibitory and/or excitatory pathways that modulate spinal transmission of nociceptive signals. Acute psychological stress has important effects on autonomic nervous activity and on hypothalamic–pituitary–adrenal axis response (particularly with regards to CRH-induced cortisol release).57 The autonomic nervous system has been implicated in stress-related GI symptoms as it can display a maladaptive response to chronic psychological stressors. A recent study demonstrated that anxiety induction increases acid-induced oesophageal hyperalgesia.58 Recent studies in rats have shown that acute stress is able to induce DIS in oesophageal mucosa. This was associated with increased mucosal permeability to small molecules and increased number of submucosal mast cells.59 It is possible, therefore, that psychological stress contributes to oesophageal hypersensitivity by central neural mechanisms and by a contributing effect of stress-induced impairment of oesophageal mucosal integrity.

It is therefore important to acknowledge that both hypersensitivity and psychological factors can lead to enhanced perception and contribute to refractoriness.

**DIAGNOSTIC TOOLS**

**Symptom evaluation**

Clarification of the actual nature of the persisting symptoms is crucial. Heartburn is characterised by pain or discomfort of burning quality that originates high in the epigastrium with intermittent cephalad retrosternal radiation. In clinical practice, many patients are referred for refractory heartburn which appears to be, after a careful interview, either epigastric burning or sore throat. In these patients, the probability of GORD-related persisting symptoms and the response rates to PPIs are lower compared with patients with typical heartburn.60

Regurgitation is an important factor of incomplete response to PPI treatment in patients with reflux symptoms. In clinical trials, the efficacy of PPIs for relief of regurgitation is considerably lower than for heartburn.61 As a consequence, a patient with both heartburn and acid regurgitation may
have adequate relief of heartburn ‘on’ PPIs but persisting regurgitation. Provided severe oesophageal motility disorders have been ruled out and GORD previously documented, these patients are probably good candidates for antireflux surgery. Physicians should also be aware that a small proportion of patients presenting with regurgitation may have gastroparesis or rumination syndrome that should be ruled out by appropriate tests, for example, gastric emptying tests and high resolution manometry-impedance,

respectively. The presence of functional GI disorders should be carefully assessed because they negatively impact on treatment of reflux symptoms. Patients with severe dyspeptic symptoms should be tested for gastroparesis. The prevalence of dyspeptic symptoms is high in patients with functional heartburn, that is, with normal oesophageal acid exposure and negative symptom—reflux association analysis. However, we have recently reported that functional dyspepsia and irritable bowel syndrome (IBS) are also strongly associated with PPI failure in patients with documented abnormal GOR with pH-impedance monitoring. Some patients may have dyspeptic symptoms that could be misinterpreted as reflux symptoms, but this is less likely to occur for IBS-like symptoms. How IBS could interfere with reflux treatment efficacy is not clear, but it may be hypothesised that persistent reflux and IBS symptoms share the same underlying mechanisms (eg, increased visceral perception) since both conditions coexist very frequently.

The presence of psychological disorders such as hysteria, anxiety and psychological distress should also be assessed in patients with refractory reflux symptoms. A systematic review of nine clinical trials reported that high levels of anxiety at baseline were associated with persistent symptoms. However, conflicting results have been recently reported and the possibility that high anxiety scores may be induced by the persisting reflux symptoms themselves cannot be ruled out. As part of the clinical evaluation, physicians should check for compliance to therapy before embarking for additional investigations. Compliance to once daily PPI in GORD has been reported to be lower in patients with refractory symptoms (46%–55%) as compared with patients with adequate relief (84%). However, a recent systematic review showed that compliance was better in patients with severe symptoms and Barrett’s oesophagus. In addition to compliance, dosing time should also be checked since taking PPIs 15 min before a meal results in a better gastric pH control although it has not been clearly demonstrated yet that it was associated with an improved clinical efficacy.

Endoscopy

Although upper GI endoscopy has low yield, it is the author’s practice to perform endoscopy in patients with refractory reflux symptoms, at least to rule out other oesophageal or gastric diseases (box 1). However, endoscopy is of relative value since most patients have normal endoscopy either because they have NERD or because the use of PPIs has healed the mucosal breaks that were initially present (though not demonstrated if the patient has not been previously scoped). As an example, it has been reported that only 6.7% of patients with refractory heartburn on once daily PPI therapy had erosive oesophagitis. Pill-induced oesophagitis and skin diseases with oesophageal involvement are rare causes of PPI refractoriness and they are usually easily differentiated from peptic ulcerations located at the lower third of the oesophagus. The presence of mucosal breaks despite PPI therapy may reflect poorly controlled acid reflux, which could be in some rare cases related to Zollinger—Ellison syndrome. If the persisting acid GOR can be considered as obvious when severe mucosal injury is observed, clinicians should be cautious in the presence of minimal lesions (erythema or increased vascularity) before establishing a link with symptoms. Again, a careful interview can help identifying the type of persisting symptoms, and additional investigations (pH-impedance monitoring on therapy) may be useful to demonstrate an association between reflux and symptoms.

When endoscopy is performed for refractory reflux symptoms, oesophageal biopsies samples should be obtained regardless of the gross appearance of the oesophageal mucosa to rule out eosinophilic oesophagitis. Upper endoscopy with biopsies has been demonstrated to be a cost-effective approach when the prevalence of eosinophilic oesophagitis is 8% or greater, but several studies suggest that this prevalence would not exceed 0.9%–4% of patients in this clinical situation. Oesophageal manometry

All patients who failed empirical management should have oesophageal manometry before reflux monitoring to position pH sensors (especially when recordings are performed on PPIs) and to rule out achalasia or severe oesophageal motor disorders. Although a ‘sphincter locator’ can be used, it is not available in many hospitals and is not as accurate as manometry to define the upper margin of the LOS, particularly in patients with hiatal hernia. Furthermore, the prevalence of heartburn has been reported to be as high as 55% in achalasia (see box 2). Ambulatory monitoring for reflux

Refractory reflux symptoms represent one of the most common indications for oesophageal testing for reflux. Patients can be tested ‘off’ therapy to confirm or rule out the presence of baseline abnormal acid reflux or ‘on’ therapy to check if reflux is responsible for persisting symptoms (box 3).

Studies ‘off’ therapy

Patients can be tested ‘off’ therapy to confirm the presence of abnormal acid reflux and/or positive symptom—reflux association; most experts consider that the added value of pH-impedance monitoring ‘off’ therapy is limited and pH monitoring alone (catheter-based or wireless)
Box 2 The role of endoscopy in refractory gastro-oesophageal reflux disease

- Diagnosis of erosive oesophagitis or Barrett’s oesophagus (<10%).
- Rule out eosinophilic oesophagitis (<4%) with at least five biopsy samples.
- Suspect severe oesophageal motility disorders (stasis, spasms).
- Suspect pill-induced oesophagitis or oesophageal lesions associated with skin diseases.

Recent advances in clinical practice

PPIs and fundoplication than patients with abnormal acid exposure although prospective data are lacking.

Perfoming ambulatory reflux testing ‘off’ therapy allows identifying patients with the so-called functional heartburn (see box 1 glossary), which is part of functional oesophageal disorders (figure 1). The ROME III definition of functional heartburn only refers to pH monitoring but the added value of impedance to pH monitoring has to be considered since using this technique a lower proportion of patients with diagnosis of functional heartburn has been reported (29% vs 39% with pH alone). Overall, studies performed with 24-h pH-impedance monitoring report 21%–40% of patients with refractory reflux symptoms as having functional heartburn.

The definitions of NERD, acid hypersensitive oesophagus and functional heartburn rely on the interpretations of the temporal relationships between symptoms and reflux events assessed with SI, symptom association probability (SAP) or both. The clinical accuracy of these indices remains a matter of debate. The agreement between SI and SAP is poor. While SAP is considered by some authors to be the best method to express the temporal relationship between symptoms and reflux episodes, SI is a simple, easy to determine parameter, and describes the proportion of symptoms that are reflux-related. SAP describes the probability that the observed relation between symptoms and reflux has not occurred by chance. For now, it cannot be stated which test should be used in clinical practice, and which should be taken into account if discrepancy exists between SI and SAP. Similarly, the adequate time window before the onset of symptoms to determine temporal association is still a matter of debate. The relevance of these indices has been recently challenged by Slaughter et al who showed that SI and SAP values were largely determined by chance occurrences unless patients refractory to PPI therapy have high rates of reflux. Although clinicians should keep in mind these shortcomings, we believe that analysis of symptom—reflux association is still clinically helpful to better identify those patients with symptoms that are related to GORD.

Studies on ‘on’ therapy

Patients with refractory symptoms are often tested ‘on’ therapy to check whether acid reflux is controlled or not by the treatment. Whether such recordings should be done under a single or double dose of PPIs is not known but most published data have been obtained in patients ‘on’ PPIs twice daily. It is generally agreed that the diagnostic yield of oesophageal pH monitoring ‘on’ PPIs for acid reflux is low since, in this situation, most reflux events are weakly acidic and therefore acid reflux is not detected. Whether prolonged wireless pH monitoring, allowing both ‘off’ and ‘on’ PPI assessments, could be useful in clinical practice remains to be further determined.
PPI therapy changes reflux patterns with a decrease in acid reflux events and an increase in weakly acidic reflux events, which represent the most prevalent type of reflux in this setting. Therefore, adding impedance to pH monitoring improves the diagnostic yield and allows better symptom analysis. Several studies have been published that used 24-h pH-impedance monitoring in refractory patients taking PPIs twice daily for which results are concordant and can be summarised as follows.\(^19\) 30 64 50%–60% of patients do not have symptoms that can be associated with GOR, 50%–40% have symptoms associated with non-acid reflux, and approximately 10% have symptoms associated with acid reflux. Based on these results, some experts advocate ‘on’ PPI testing to document that GORD is not the cause of persisting symptoms and that other causes should be considered and further investigated.\(^91\) However, the accuracy of SI/SAP indices for weakly acidic reflux events ‘on’ PPIs has not yet been clearly established and there are no outcome data to support this strategy; whether other impedance parameters such as oesophageal bolus exposure and/or high number of reflux episodes should be taken into account remains to be determined. Pritchett et al have reported that 36% of patients with refractory symptoms had an abnormally high number of reflux events ‘on’ PPI.\(^63\) While Zerib et al reported rates of 8.4% and 21.1% of excessive numbers of reflux events and increased oesophageal bolus exposure, respectively.\(^90\) In a study in 80 patients with refractory heartburn, 53% of the patients had a negative symptom association analysis ‘on’ PPI, but only 35% of the patients were considered to have a normal recording when an abnormally high number of reflux episodes detected by impedance was taken into account.\(^92\) This study also suggests that patients with refractory heartburn and negative symptom association indices during pH-impedance monitoring performed on therapy should probably be considered as having functional heartburn if they meet the other diagnostic criteria. Unfortunately, there is virtually no outcome study that could help to determine the best parameter to be used in clinical practice; moreover, there is currently only one set of normal pH-impedance values ‘on’ PPI twice daily published as an abstract form.\(^93\)

Mainie et al have reported favourable results of laparoscopic fundoplication in 18 of 19 patients with persistent symptoms despite PPI therapy and positive SI for non-acid reflux on oesophageal pH-impedance monitoring.\(^94\) It is currently the only available study suggesting that pH-impedance monitoring could have a significant impact on the management of GORD in patients who fail adequate acid suppressive therapy. Further controlled prospective outcome studies are urgently needed to confirm these results. It seems reasonable to propose that before embarking on pH-impedance recordings ‘on’ PPI, the presence of GORD should have been previously demonstrated by endoscopy and/or pH monitoring ‘off’ therapy.

The role of DGOR has been suggested by several studies but, when considering the relatively low diagnostic yield of bilimetry together with the limited commercial availability of the equipment, bilirubin oesophageal monitoring does not appear to be a first choice for oesophageal testing in patients with refractory reflux symptoms.

**THERAPEUTIC OPTIONS**

**Lifestyle modifications**

Diet and lifestyle modifications like weight loss, head of bed elevation and avoiding late-night meals are effective interventions for GORD.\(^95\) 96 More recently, actively training the diaphragm by breathing exercise has been shown to improve GORD as assessed by pH-metry, quality of life scores and PPI usage.\(^97\) However, whether these interventions may be useful in patients with refractory reflux symptoms remains to be demonstrated. A recent study found that lifestyle modifications were significantly less frequently implemented by patients who report lack of response to standard dose PPI treatment than responders to standard dose PPI, but the difference was not statistically significant for patients who failed PPIs twice daily.\(^70\) The role of diet is frequently advocated by patients with reflux symptoms who failed PPI therapy but there is no clear evidence for a benefit of excluding specific foods (eg, acidic or spicy foods). As fat can increase oesophageal sensitivity to acid, heavy meals are usually avoided spontaneously by the patients themselves. In fact, in clinical practice it is important to reassure the patient concerning the harmless effects of many foods and to convince him/her to avoid too restrictive dietary regimens.

**Antisecretory drugs**

Nowadays, most patients with reflux symptoms will receive, sooner or later, a once daily PPI therapy. If adequate symptom relief is not achieved,
after compliance and dosing time have been checked and before embarking for additional investigations, several therapeutic strategies can be proposed. Switching to another PPI is frequently tested by physicians, and though no strong scientific data (neither pharmacological nor clinical) support this strategy, it has proven to be effective in routine clinical practice. To date, two studies, one uncontrolled and one randomised, favour a switch to esomeprazole when another PPI brand failed. This option could even be cost-effective. Doubling the dose of PPI is very common though, again, virtually no data support this strategy. Two randomised studies demonstrated that when a single dose of lansoprazole (30 mg once daily) failed, switching to either omeprazole or esomeprazole as lansoprazole 30 mg twice daily. In these studies, approximately 20%–30% of patients could achieve adequate symptom control after 6–8 weeks of therapy. Therefore, doubling the dose of PPI is probably a valid option (though not approved) in clinical practice, provided the dose is given twice daily before breakfast and dinner, as supported by gastric pH studies.

Finally, attempts have been made to improve either the onset of action or the antisecretory effect of these compounds but the results in terms of clinical efficacy have been disappointing. Studies with dexlansoprazole MR have failed to demonstrate any clinically significant improvement in both healing rates of oesophagitis and symptom control. Potassium-competitive acid blockers block the proton pumps via a different mechanism than conventional PPIs that is competing with binding of $\mathrm{K}^+$. Despite a rapid onset of action to inhibit gastric acid secretion, two large clinical trials with AZD0865 (revaprazan) failed to demonstrate any significant improvement in healing rates and symptom control in patients with reflux oesophagitis and the development of this compound has been stopped. It is of note that these new compounds have not been tested in refractory reflux patients.

**Add-on therapies with PPIs**

For the time being, there are no data supporting the use of prokinetics as add-on therapy in patients with refractory reflux symptoms while adding alginate (spontaneously done by many patients) to omeprazole 20 mg has been recently shown to improve symptom control.

Nocturnal gastric acid breakthrough occurs in more than 75% of patients taking PPIs twice daily and adding histamine 2 receptor antagonists (H2RAs) at bedtime has been shown to improve nocturnal gastric acid control in GORD patients. Whether this translates into improved clinical efficacy has not yet been clearly established. Indeed, the only available clinical data come from a retrospective uncontrolled study that reports overall symptom improvement in 72% of patients. Moreover, conflicting results have been reported regarding decreased efficacy of H2RAs after long-term treatment. Based on these results and personal experience, several experts, mainly from the USA, advocate the intermittent or on-demand use of H2RAs at bedtime.

Transient lower oesophageal sphincter relaxations (TLOSRs) represent the main mechanism of all type of reflux, that is, both acid and weakly acidic reflux episodes and, therefore, controlling the occurrence of TLOSRs appears to be a relevant therapeutic objective in GORD. For the time being, the only compound available for human use that can decrease TLOSRs occurrence is baclofen, a GABAB agonist used for many years for the treatment of spasticity. Mechanistic studies and short-term therapeutic trials in healthy controls and in patients with GORD have confirmed the efficacy of baclofen in reducing TLOSRs, reflux events and reflux symptoms. Two studies of chronic administration of baclofen in GORD patients confirmed its efficacy to improve reflux-related symptoms. Ciccaglione and Marzio showed that baclofen at a dose of 10 mg three times a day as monotherapy significantly reduced the number of acid reflux episodes together with the oesophageal acid exposure and improved reflux-related symptoms in 18 GORD patients. Koek et al performed an open study in 16 patients with persistent symptoms despite PPI therapy and abnormal DGOR. These authors report a decrease in oesophageal bile exposure and a significant symptomatic improvement with PPIs and add-on therapy with baclofen at a dose progressively increased from 5 to 20 mg three times daily at meals. The critical issue with GABAB agonists is tolerability. Many patients report CNS side effects such as dizziness, drowsiness, nausea and vomiting which seriously limit the use of this compound in routine practice. A number of GABAB agonists with improved tolerability have been developed such as arbaclofen placarbil or lesogaberan but have been abandoned mainly because of limited clinical efficacy. As an example, lesogaberan as add-on therapy with PPIs in patients with refractory symptoms resulted in a low (though significant) 16% remission rate as compared with PPIs alone (8% remission rate). Similarly, a negative allosteric modulator of mGluR5 receptor (ADX10059) as monotherapy has been shown to improve GORD symptoms and the occurrence of reflux events but failed to demonstrate a significant clinical efficacy in refractory GORD patients and the further development of this compound has been halted.

To summarise, baclofen is currently the only available compound that can be helpful to reduce the occurrence of TLOSRs and control refractory reflux symptoms as add-on therapy with PPIs, but its use is limited by a poor tolerability.

**Pain modulators**

Most patients with persisting symptoms despite PPI therapy have a normal oesophageal exposure to acid and bolus and probably have oesophageal hypersensitivity. Although symptoms cannot be
clearly related to any type of reflux, such as oesophageal hypersensitivity has also been demonstrated in patients with functional heartburn. In the context of visceral hypersensitivity, the use of pain modulators may be attractive since tricyclic antidepressants, trazodone and selective serotonin reuptake inhibitors have all been shown to improve oesophageal pain in patients with non-cardiac chest pain. It is believed that these agents, used in non-mood-altering doses, confer their visceral analgesic effect by acting at the central nervous system and/or sensory afferents level. In a randomised placebo-controlled study, citalopram 20 mg once daily for 6 months has been shown to be effective in patients with acid hypersensitive oesophagus and refractory GOR symptoms. Other compounds may potentially exert an influence on visceral perception which may be exploited in refractory reflux symptoms. Tegaserod, a 5-HT₄ agonist, has been shown to decrease oesophageal and gastric symptoms in a placebo-controlled crossover trial conducted in patients with overlapping symptoms of GORD and functional dyspepsia. In the same study, tegaserod increased the pressure threshold for gastric pain and may therefore be effective through modulation of visceral perception. Since upregulation in nerve fibres of acid-sensing ion channels such as TRPV-1 has been demonstrated, antagonists of the TRPV-1 receptor (AZD1386) have been recently developed and proof-of-concept studies recently reported. In healthy humans, AZD1386 increased oesophageal and skin heat pain thresholds and was well tolerated. Therefore, this new class of drug may have a potential in NERD and refractory heartburn as well but it is too early to extrapolate from pharmacodynamic effects to the clinic.

**Endoscopic therapy**

To our best knowledge, there are only two antireflux endoscopic devices that are still currently available for human use, that is, the Stretta procedure and the EsophyX transoral incisionless fundoplication. The Stretta procedure (radiofrequency energy delivery) could be effective in decreasing oesophageal sensitivity to acid. It is suggested by several controlled clinical studies which showed clinical improvement of oesophageal symptoms and decrease in PPI use despite no significant effect on oesophageal acid exposure and demonstrated experimentally by one study. Therefore, the Stretta procedure may be considered as a ‘pain modulator’ technique and should be tested in hypersensitive oesophagus, functional heartburn and in patients with persisting symptoms despite PPIs.

Transoral incisionless fundoplication using EsophyX offers a less invasive alternative to laparoscopic fundoplication that has been, as many other endoscopic approaches, mainly evaluated in PPI dependant GORD patients. However, two studies in patients with refractory reflux symptoms have been recently reported. A short (10 patients) prospective study showed that EsophyX normalised acid reflux parameters in only 50% of patients (as compared with 100% in patients with laparoscopic fundoplication) and that seven out of 10 patients had partial or no symptom remission (vs 10/10 in the surgical group). A larger but retrospective study in 110 patients reported a 72% remission rate with the EsophyX procedure after a median follow-up of 7 months. Therefore, the potential value of this technique should be further evaluated in controlled prospective trials.

**Antireflux surgery**

There is no doubt that laparoscopic fundoplication is a very effective therapy to control acid and non-acid GOR and a recent multicentre randomised study demonstrated that antireflux surgery and esomeprazole achieved similarly high remission rates at 5 years in patients in whom symptoms were initially well controlled by the PPI therapy. Although failure of PPIs is one of the most common indications for antireflux surgery, it is generally considered by experts that antireflux surgery in these patients has less favourable clinical outcome compared with that obtained in patients with adequate PPI symptom control. As an example, together with normal acid exposure and presence of atypical reflux symptoms, persisting symptoms on PPIs have been shown to be a factor associated with poor postoperative outcome. However, conflicting results have been reported, showing that favourable outcomes could be achieved in patients with inadequate response to PPI therapy. In the absence of proven obvious oesophagitis (ie, presence of mucosal breaks), it seems relevant to document pathological GOR and/or positive reflux symptom association before embarking to antireflux surgery. Whether this evaluation should be performed ‘off’ or ‘on’ PPIs remains to be determined. Regarding studies ‘off’ therapy, abnormal oesophageal exposure time has been demonstrated to be a predictor of favourable postoperative outcome, irrespective of the symptom association analysis. Indeed, a recent study reported similar 5-year postoperative outcomes in patients with positive and negative SI/SAP, but with abnormal oesophageal acid exposure, preoperatively. Good postoperative outcomes have also been reported when oesophageal acid exposure is within the normal values in patients with a positive symptom association analysis. One study reported favourable outcomes in patients with normal acid exposure but abnormal number of reflux episodes detected by oesophageal-impedance monitoring. Data on preoperative assessment ‘on’ PPIs are scarce. Frazzon et al reported good results in 38/40 patients refractory to PPIs in whom pH-impedance monitoring demonstrated either abnormal numbers of reflux episodes or positive symptom association analysis. Mainie et al have reported favourable results of laparoscopic fundoplication in 18 of 19 patients with persistent symptoms despite PPI therapy and positive SI for non-acid reflux on oesophageal pH-impedance monitoring.
To summarise, surgery can be a valuable option in patients with typical reflux symptoms with inadequate response to PPIs, provided abnormal oesophageal acid exposure and/or positive symptom association analysis can be demonstrated ‘off’ PPI therapy. The added value of 24-h pH-impedance monitoring performed ‘on’ PPIs remains to be further determined by prospective outcome studies.

**MANAGEMENT OF PATIENTS WITH REFRACTORY REFUX SYMPTOMS**

**Empirical management**

Patients presenting with refractory reflux symptoms can be initially managed empirically. A careful interview is mandatory to determine the nature of symptoms that were initially present and of those that persist on therapy, and to identify which one is considered to be troublesome by the patient. It is important to pay specific attention to the symptom ‘heartburn’ which may in fact correspond to sore throat or epigastric burning. Likewise, many patients report dyspeptic symptoms that were initially present and have been unmasked by the PPI therapy. If atypical reflux symptoms or severe dyspeptic symptoms are diagnosed, a specific work up is mandatory. If typical reflux symptoms persist, that is, heartburn and regurgitation, compliance and dosing time should be checked, since taking PPIs before meals provides a better gastric acid secretion control. Though not supported by strong clinical data, switching to another PPI brand may be an option before doubling the dose. Twice daily PPIs (single dose taken before breakfast and before dinner) is not an approved dose by health authorities but could achieve adequate symptom control after 6–8 weeks of therapy in approximately 20%–30% of patients with inadequate symptom control on once daily PPI. If clinical remission is achieved, titration can be proposed after 2–3 months of double dose therapy. In case of failure, adding alginates or H2RAs at bedtime may be tested, but one has to keep in mind that H2RAs should better be taken on demand or intermittently to avoid tolerance (box 4).

**Endoscopy and functional investigations**

Patients with persisting reflux symptoms despite a 2-month double dose PPI therapy should be further investigated. An upper GI endoscopy with at least five oesophageal biopsies should be performed to rule out other oesophageal gastric diseases such as eosinophilic oesophagitis, pill-induced oesophagitis or skin diseases associated with oesophageal involvement. The persistence of mucosal breaks in patients ‘on’ PPI therapy is rare (<10%) and may reflect poorly controlled acid reflux. If erosive oesophagitis is observed in patients on double dose PPIs for at least 2 months, GORD can be considered as being documented. Although data to support this proposition are lacking, it may be useful to perform pH-impedance ‘on’ PPIs in these patients (1) to demonstrate an association between persisting symptoms and reflux if only minimal lesions are present and (2) to assess the efficacy of gastric acid secretion (when simultaneous gastric and oesophageal pH monitoring is available). Patients in whom GORD has been previously demonstrated with adequate relief of heartburn but persisting regurgitation should be considered for surgery, provided severe oesophageal motility disorders have been ruled out by oesophageal manometry. Likewise, achalasia or severe motility disorders can be suspected if oesophageal stasis and/or cardial spasm. Therefore, oesophageal manometry should be performed to position pH or pH-impedance catheters and to rule out achalasia (figure 2).

In most patients, upper GI endoscopy is normal, and ambulatory monitoring for reflux is mandatory that can be performed ‘off’ or ‘on’ PPI therapy.

Ambulatory reflux monitoring ‘off’ therapy should be considered for patients in whom GORD has not been previously documented by endoscopy and/or pH monitoring. GORD can be demonstrated by the means of catheter-based 24-h pH monitoring, but 48–96-h wireless capsule pH monitoring and 24-h pH-impedance monitoring have been shown to have increased diagnostic yield. Recordings ‘off’ PPIs allow classifying the patients as having NERD, acid sensitive oesophagus or no reflux (or functional heartburn). The best symptom association index and the optimal time window for the analysis are yet to be determined.

Ambulatory reflux monitoring ‘on’ PPIs twice daily can be proposed to patients with documented GORD to establish a correlation between refractory symptoms and reflux events and/or to exclude GORD as the cause of the persisting symptoms. Regarding the low diagnostic yield of pH alone recordings ‘on’ PPIs twice daily, the use of 24-hour pH-impedance monitoring is recommended. Based on the only available outcome data with pH-impedance on therapy, correlation between refractory symptoms and reflux should rely on an SI value above 50%. However, should other parameters (such as SAP, oesophageal bolus exposure or the total number of reflux events) be taken into account remains to be further determined. When both SI and SAP are positive, the probability that the residual symptoms are related to GORD is high. When both symptom association indices are negative, GORD is probably not the cause of the remaining symptoms and whether this situation could be assimilated to functional heartburn

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**Box 4 Initial empirical management of refractory gastro-oesophageal reflux symptoms**

- Careful interview to assess the nature of residual symptoms.
- Check for compliance.
- Check for dosing time (15–30 min before meals).
- Double the dose (before morning and evening meals) for 2 months.
- Add-on therapy with alginates.
- Add-on therapy with histamine 2 receptor antagonists at bedtime (on demand or intermittently to avoid tolerance).
Added value of pH-impedance monitoring

Oesophageal pH-impedance monitoring is considered to be ‘positive’ (symptoms are related to reflux) when both symptom index (SI) and symptom association probability (SAP) are higher than 50% and 95% respectively and ‘negative’ (symptoms are not related to reflux) when both SI and SAP are lower than 50% and 95%. Non-concordant SI and SAP should be interpreted with caution before proposing antireflux surgery. TLOSR, transient lower oesophageal sphincter relaxation. SSRI, selective serotonin reuptake inhibitors.

Therapeutic options in patients with documented GORD

Most patients without documented GORD belong to the functional heartburn group. Functional heartburn is a functional GI disorder characterised by symptoms of heartburn not related to GOR. Addition of impedance measurement to pH-monitoring is likely to increase the number of patients with recognised reflux-related symptoms. The pathophysiology of functional heartburn remains largely unknown but involves disturbed oesophageal perception and psychological factors such as depression, anxiety and somatisation. The treatment of functional heartburn remains largely empirical and an individual approach is therefore recommended. The use of pain modulators is recommended by most experts despite the lack of appropriate clinical trials to support it. Similarly, psychological approaches such as behavioural modification or relaxation therapy may be beneficial but, to date, no published controlled trials demonstrate efficacy of any of these interventions in functional heartburn patients.

CONCLUSION

Most patients with refractory reflux symptoms do not have abnormal oesophageal acid exposure. Multiple pathophysiological mechanisms have been proposed to account for the persistent symptoms. To better understand these mechanisms, research comparing data from PPI responders versus PPI non-responders is mandatory (box 5).

The diagnostic evaluation consists of excluding alternative diagnoses and demonstrates a positive reflux–symptom association during reflux monitoring studies. The current algorithms for reflux–symptom analysis have important shortcomings and there is an urgent need for outcome studies that will help to identify the pretreatment statistical algorithm that best predicts the outcome.

Several new classes of medications are under investigation. They focus on the following targets: further improving suppression of gastric acid secretion, decreasing TLOSR rate, improving oesophago-gastric motility (prokinetics), improving oesophageal mucosal resistance and developing oesophagus-specific pain modulators. Endoscopic treatments can affect distal oesophageal innervations reducing sensitivity (Stretta) and/or reducing reflux volume and proximal extent, both factors being considered critical for persistent reflux control in patients with persisting reflux symptoms. The poor tolerability of baclofen limits its use in routine practice and, therefore, the dosage should be increased very progressively to reach 30–40 mg daily. In patients with acid sensitive oesophagus and inadequate response to PPIs, switching to citalopram 20 mg daily has been shown to be a valid option. Endoscopic therapies such as the Stretta procedure and the EsophyX transoral incisionless fundoplication may prove to be effective in the future.
Box 5 Research agenda

Pathophysiology
Evaluate differences between proton pump inhibitor (PPI) responders and PPI-refractory patients in:
- Distribution of gastric contents (proximal stomach and acid pocket).
- Obesity and gastro-oesophageal pressure gradients.
- Gas reflux and other non-acidic components of the refluxate.
- Changes in mucosal integrity in response to reflux (in biopsies and in vivo).
- Detection of microscopic mucosal changes with endoscopic techniques.
- Mucosal receptors and mediators involved in pain sensitivity.
- Role of the autonomic nervous system.
- Functional brain imaging in response to oesophageal stimulation.

Ambulatory monitoring for reflux
- Determine the best symptom association analysis (symptom index, symptom association probability time window).
- Establish normal pH-impedance values ‘on’ PPIs twice daily.
- Determine the clinical relevance of pH-impedance monitoring ‘on’ PPIs twice daily with appropriate outcome data.
- Determine the relevance of prolonged (96 h) off and on therapy recordings.

Treatment to be further developed
- Transient lower oesophageal sphincter relaxation inhibitors and prokinetics (5-HT₄ agonists).
- Endoscopic therapy (Stretta, EsophyX).
- Topical mucosal protectors.
- Pain modulators (Selective serotonin reuptake inhibitors (SSRIs), transient receptor potential vanilloid 1 antagonists).
- Psychological approach (hypnosis, relaxation therapy).
- Controlled, randomised study of antireflux surgery in refractory gastro-oesophageal reflux disease.

perception. Finally, the role of antireflux surgery for patients with incomplete response to PPIs remains controversial. A controlled, randomised study including a significant number of well-selected patients (excluding functional heartburn) with prolonged follow-up to account for placebo effects is mandatory to establish the real efficacy of surgery in these patients.

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REFERENCES
3. Inadomi JM, McEntyre L, Bernard L, et al. Step-down from multiple- to single-dose proton pump inhibitors (PPIs):


Recent advances in clinical practice


118. Castell DD, Zeribib F, Bruley des Varannes S, et al. Efficacy and tolerability of ADX10059, a mGluRs negative allosteric modulator, as add on therapy to proton pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD). Gastroenterology 2011;140:S-577.


Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors

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