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Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease – where next?

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SUMMARY

Proton-pump inhibitor failure has become a common clinical dilemma in gastrointestinal clinics and has been increasingly encountered at the primary care level as well. Underlying mechanisms are diverse and may overlap. Most patients who have proton-pump inhibitor failure are likely to originate from the non-erosive reflux disease phenotype. Currently, available diagnostic modalities provide limited clues to the exact underlying cause. Treatment relies primarily on escalating dosing of proton-pump inhibitors. However, new insights into the pathophysiology of proton-pump inhibitor failure are likely to provide alternative therapeutic options.

INTRODUCTION

Since their introduction into the market almost two decades ago, proton-pump inhibitors (PPIs) have revolutionized the treatment of gastro-oesophageal reflux disease (GERD). The marked progress that has been achieved in symptom resolution and oesophageal mucosal healing has positioned the PPIs as the most potent class of drugs for the treatment of GERD.

Despite their high degree of efficacy, clinical failure in GERD patients has been reported. In fact, the prevalence of PPI failure has increased in proportion with the expanding indications for their use. It has been estimated that about 30% of GERD patients remain symptomatic on standard (once daily) dose of PPI. Of these patients, the vast majority will continue to experience GERD symptoms on even higher doses of PPI.

The PPI failure has become a very common clinical dilemma in gastrointestinal (GI) clinics and has been increasingly encountered at the primary care level as well. Furthermore, as more primary care providers feel comfortable prescribing PPIs as the first-line of treatment for GERD, PPI failure will become even more prevalent in primary care and GI practice. This is compounded by the increased availability of PPIs as an over-the-counter (OTC) and generic compounds. Moreover, broader indications for PPIs and frequent administration by doctors for a variety of upper GI symptoms will inevitably result in more treatment failures. Presently, PPI failure has become one of the main clinical challenges in GERD management that gastroenterologist have to address in their practice almost on a daily basis. Whilst cost analysis of PPI failure has yet to be carried out, it is likely an expensive clinical problem because patients tend to repeatedly utilize health care resources such as clinic visits, diagnostic studies and prescription medications.

The purpose of this review is to identify the underlying mechanisms of PPI failure and to delineate a diagnostic and therapeutic algorithm for these patients.

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METHODS

A review of the medical literature was conducted to identify original studies evaluating the effect of PPIs in patients with GERD. Medline and PubMed were

searched for English language articles that were published between 1985 and 2005. The terms used for the online bibliographic search included: PPI, GERD, oesophagitis, Barrett's oesophagus, esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole. Additional articles were identified through a manual search and from other doctors and experts in the field.

DEFINITION OF PPI FAILURE

Presently, the medical literature does not offer an accepted definition of PPI failure. This is compounded by the popular usage of the term 'refractory GERD', which is less specific but indicates a similar clinical situation.[1] PPI studies commonly last 8 weeks in erosive oesophagitis and 4 weeks in non-erosive reflux disease (NERD) or symptomatic GERD. In erosive oesophagitis therapeutic trials, the primary clinical end-points are symptom resolution and healing of the oesophageal mucosa. In NERD or symptomatic GERD, symptom improvement is usually the sole clinical end-point. PPI failure in erosive oesophagitis used to be determined by the persistence of oesophageal inflammation despite a full course of PPI therapy. Subsequently, it was recognized that healing of erosive oesophagitis may not be necessarily indicative of complete resolution of GERD symptoms (infra vide).[2] In other words, patients may continue to report GERD symptoms despite complete healing of oesophageal mucosa (up to 15%). The percentage of patients that report complete resolution of GERD symptoms despite the persistence of oesophageal erosions while taking PPIs is unknown. On the other hand, up to 50% of the patients with erosive oesophagitis that relapse symptomatically on PPI once a day lack any evidence of concomitant relapse of oesophageal inflammation.[3]

In patients with NERD, traditional clinical end-points such as complete resolution of GERD symptoms may not be readily achievable. 'Softer' clinical end-points have been adopted in NERD studies, allowing patients to experience some level of symptoms. Regardless of any arbitrary definition of PPI failure, patients will eventually determine success of therapy. This may obviously vary from one individual to another, based on patient's expectations from therapy, which is likely to be influenced by gender, age, ethnic background, social status, education, country of origin and other important demographic factors.

In a recent study of patients with uninvestigated GERD, PPI failure was defined as patients who continued to report heartburn symptoms of any severity for at least 2 days/week during the last 30 days.[4] In another study, therapeutic failure of standard dose PPI was considered, if patients continued to experience heartburn episodes more than once a week, for the last 3 months.[5]

For the purpose of this discussion, we propose the following definition of PPI failure: 'patients who failed to obtain complete oesophageal healing and/or satisfactory symptomatic response after a full course of standard dose PPI (once a day)'. This definition allows inclusion of patients who perceived their remaining symptoms on PPI therapy as bothersome, independent of frequency or severity.

THE EXTENT OF THE PROBLEM

Whilst the American College of Gastroenterology, practice guidelines in GERD stated that '…GERD refractory to medical treatment is very rare', recent studies have challenged this assertion.[6] Inadomi *et al.* evaluated 298 consecutive patients in a heartburn clinic and found that 42.3% required more than PPI once a day to control their symptoms.[7]

In a study performed at a primary care level with community-based patients, Carlsson *et al.*[8] evaluated the efficacy of omeprazole 20 mg once daily in 225 patients with and without erosive oesophagitis for a period of 4 weeks. After 4 weeks of treatment, 41% of the patients reported complete symptom resolution and 73% obtained sufficient symptomatic relief. The authors of the study suggested that 27% of all patients with GERD will continue to be symptomatic on PPI once a day after 4 weeks of treatment.

A study in 11 064 chronic heartburn patients found that PPIs were the preferred class of medications among GERD patients for preventing heartburn. However, only 58% of PPI recipients reported being totally satisfied with their antireflux treatment. The authors concluded that even with PPIs there is room for improvement in therapy outcomes.[9]

In general, it appears that the prevalence of PPI failure differs from patients with NERD and those with erosive oesophagitis. However, studies in the different phenotypic presentations of GERD suggest that the overall prevalence of PPI failure is approximately 30%.

PPI FAILURE IN THE DIFFERENT GERD GROUPS

To understand which patients are likely to fail PPI therapy, in this review we will assess the three phenotypic presentations of GERD separately (Figure 1). This is supported by natural course studies, demonstrating that most patients with NERD (85–90%) do not progress overtime to develop erosive oesophagitis or Barrett's oesophagus and those with erosive oesophagitis are unlikely to progress overtime to Barrett's oesophagus.[10] It is essential to determine, from which phenotypic presentation of GERD most PPI failure patients originate. Identifying the main source of this challenging group of patients may help to develop proper diagnostic techniques and tailor better therapy.

Non-erosive reflux disease

Studies have demonstrated that up to 70% of patients with typical symptoms of GERD, in a primary care setting, have NERD. As a result, NERD is considered the most common presentation of GERD.

A number of studies evaluated the efficacy of PPIs in NERD patients. In a multicentre, randomized, double-blind study, omeprazole 20 mg once daily was compared with placebo in controlling symptoms of 209 patients with NERD.[11] After 4 weeks of therapy, 57% of patients in the omeprazole group were free of heartburn, 75% free of acid regurgitation and 43% were completely asymptomatic. In another study, NERD patients were randomized to omeprazole 20 mg/day; omeprazole 10 mg/day; or placebo.[12] The study authors found that at 4 weeks 46% of patients treated with omeprazole 20 mg/day, 31% treated with omeprazole 10 mg/day and 13% of those who received placebo reported complete relief of heartburn. Miner *et al.* enrolled 203 patients with NERD who were randomized to either rabeprazole 20 mg once daily or placebo. After 4 weeks only 56.7% of the patients receiving rabeprazole reported satisfactory symptom relief when compared with 32.2% of those receiving placebo ($P < 0.008$).[13]

In general, the proportion of NERD patients responding to a standard dose of PPI is approximately 20–30% lower than what has been documented in patients with erosive oesophagitis. In a systematic review of the literature, PPI symptomatic response pooled rate was 36.7 (95% CI: 34.1–39.3) in NERD patients and 55.5 (95% CI: 51.5–59.5) in those with erosive oesophagitis.[14] Therapeutic gain was 27.5% in NERD as

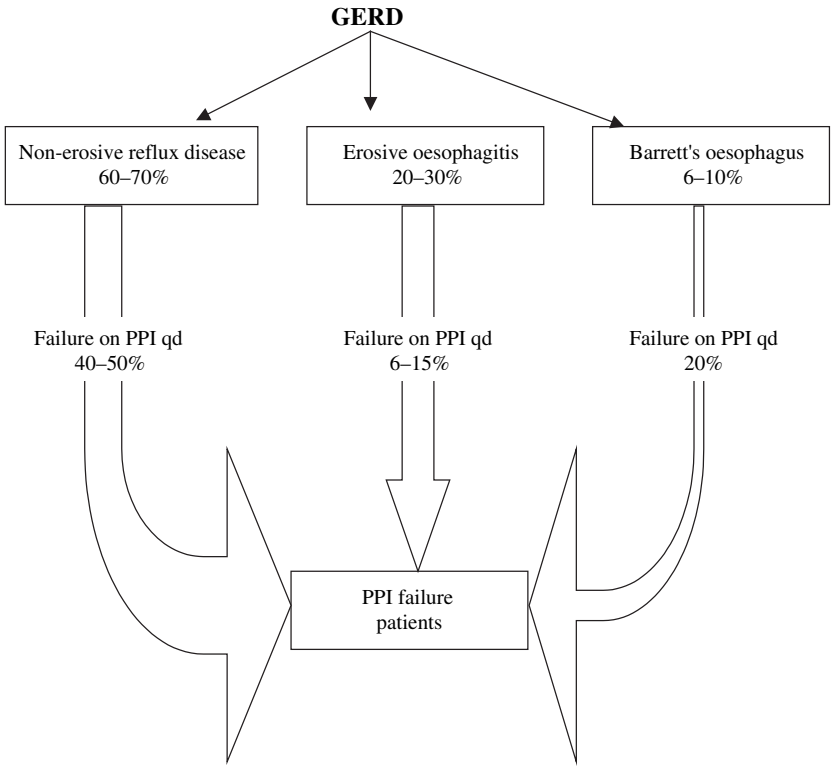

Figure 1. The proportion of patients that failed symptomatically proton-pump inhibitor (PPI) once daily in each of the gastro-oesophageal reflux disease (GERD) groups. The non-erosive reflux disease (NERD) group, which accounts for most of the patients with GERD and demonstrates the lowest response rate to PPI once daily, is the main contributor for the PPI failure phenomenon.

compared with 48.9% in erosive oesophagitis. Furthermore, patients with NERD demonstrate a direct relationship between response to PPI therapy and degree of oesophageal acid exposure. The greater the distal oesophageal acid exposure, the higher the proportion of NERD patients reporting symptom resolution.[12] This is the opposite of what has been observed in patients with erosive oesophagitis, where the greater the oesophageal inflammation the lower the response rate to PPI once daily. Patients with NERD also demonstrate longer lag-time to sustained symptom response when compared to patients with erosive oesophagitis (two- to threefolds).

Studies have shown that about 30–50% of the NERD patients demonstrate oesophageal acid exposure within the physiological range. Patients with NERD and abnormal pH testing demonstrate a 55% overlap of total time pH < 4 when compared to those with erosive oesophagitis and 50% when compared to those with Barrett's oesophagus.[15] Moreover, the therapeutic response to PPI once daily of the NERD patients with abnormal pH testing appears to be similar to the response rate of patients with erosive oesophagitis (75–85%).[12]

Patient with NERD and normal pH testing have been termed functional heartburn, defined as 'episodic retrosternal burning in the absence of pathological GER, pathology-based motility disorders, or structural explanations'.[16] The functional heartburn group is further divided into two subgroups. The first group includes patients with close temporal relationship between their heartburn symptoms and acid reflux events, in spite of physiological range of oesophageal acid exposure. This subgroup accounts for up to 40% of the patients with functional heartburn and has been termed the hypersensitive oesophagus.[17] Patients with hypersensitive oesophagus demonstrate partial response to PPI treatment.[18] In contrast, the other subgroup demonstrates lack of any correlation between heartburn episodes and acid reflux events. These patients are unlikely to respond to any antireflux intervention. Factors other than acid reflux are likely responsible for these patients' symptoms.

Patients with functional heartburn demonstrate the lowest symptom response rate to PPI once daily when compared with the other NERD patients. Lind *et al.* showed that only 45% of functional heartburn patients reported sufficient relief of heartburn symptoms when compared with other NERD patients.[12] Consequently, the functional heartburn group is likely responsible for the low response rate of NERD patients to PPI once daily when compared to patients with erosive oesophagitis. The functional heartburn patients are also responsible for lack of difference in symptom response rate between NERD patients on half standard dose PPI once daily and those on full standard dose PPI once daily.[19] Recognizing that NERD is the most common presentation of GERD, affecting up to 70% of the community-based GERD patients, and of those up to 50% are functional heartburn patients, who demonstrate the lowest response rate to PPI once daily, then one can conclude that many of the PPI failure patients originate from the NERD group, primarily the functional heartburn group.

Erosive oesophagitis

Studies in patients with erosive oesophagitis, treated with a PPI once daily, showed 88–96% healing rates after 8 weeks of therapy, regardless of the brand of PPI that was used and the underlying severity of erosive oesophagitis.[2, 20–22] As a result, it appears that only 4–12% of the patients with erosive oesophagitis fail PPI once a day. As expected, patients with more severe grades of erosive oesophagitis have demonstrated a higher PPI failure rate than those with less severe disease. In one study[21] that included 1284 patients with erosive oesophagitis that were treated with two different PPIs once daily, 10.6–11.8% of those with grade 2 erosive oesophagitis failed healing after 4 weeks of treatment, when compared with 26.5–30.2% of those with grades 3 and 4. Richter *et al.* demonstrated that the failure rate of patients with erosive oesophagitis receiving either omeprazole 20 mg once daily or esomeprazole 40 mg once daily was 9.6% and 6.6% for Los Angeles grade A; 28.7% and 10.6% for grade B; 29.6% and 12.8% for grade C; and 36.2% and 20% for grade D, respectively[23] (Figure 2).

Whilst PPIs are also very effective in providing symptomatic relief in patients with erosive oesophagitis, there is a 10–15% discrepancy between symptom resolution and mucosal healing.

Knowing that erosive oesophagitis affects approximately 30% of the patients with GERD and most of the subjects suffer from mild to moderate erosive disease then it is unlikely that erosive oesophagitis patients contribute most of those who fail PPI once daily.

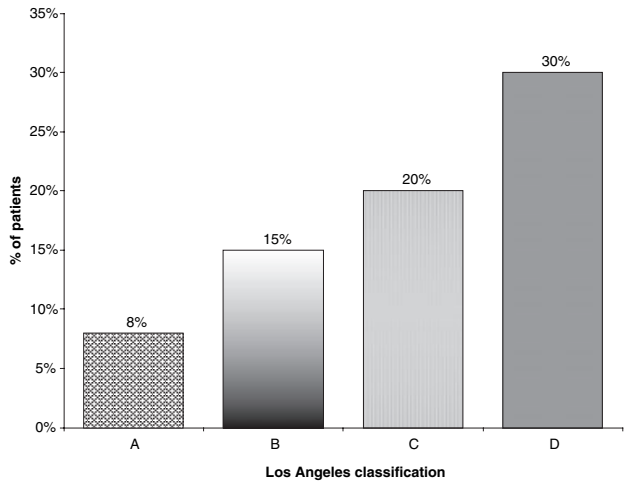

Figure 2. Proportion of healing failure in patients receiving proton-pump inhibitor once a day according to patients baseline grading of erosive oesophagitis.[88]

Barrett's oesophagus

The prevalence of Barrett's oesophagus is 6–12% of all patients who present for endoscopy with GERD-related symptoms, and 0.25–3.9% in unselected cases undergoing upper endoscopy.[24] As a group, patients with Barrett's oesophagus have demonstrated the highest level of acid exposure in the distal oesophagus when compared to those with NERD or erosive oesophagitis,[17] suggesting the need for more aggressive antireflux treatment. Furthermore, there is a close correlation between the length of Barrett's oesophagus and extent of oesophageal acid exposure.[25] Although the rates of symptom relief in patients with Barrett's oesophagus who receive treatment with a PPI approach 80%, there is a discrepancy between symptom resolution and acid control in such patients. It has been shown that 20–40% of the patients with Barrett's oesophagus whose symptoms resolved during PPI treatment, still demonstrate abnormal oesophageal acid exposure, by 24-h oesophageal pH monitoring.[26, 27] This phenomenon has been described even when high doses of PPI (up to four times daily) were used[28] and appears to be independent of patients' symptom resolution. Katzka and Castell showed that of five Barrett's oesophagus (BE) patients receiving omeprazole daily (20–60 mg) and reporting complete symptom resolution, four (80%) continued to have an abnormal oesophageal acid exposure.[26] Similarly, Fass *et al.* demonstrated that of 25 BE patients receiving omeprazole 40 mg twice daily almost a quarter were still having abnormal acid exposure and of those 67% were symptom-free.[28] In clinical practice; however, doctors will target symptom resolution in patients with BE, which may well be insufficient to control oesophageal acid exposure in a significant minority. It is unclear if the persistence of abnormal acid exposure in patients with Barrett's oesophagus on high-dose PPI should be further addressed therapeutically. Thus far, there is no clear evidence that increased PPI dosing is necessary in this situation. There are currently no data to support survival benefit with acid reduction therapy and there is no consensus as to whether the treatment end-point in patients with Barrett's oesophagus should be complete acid control. Although, recent data suggested that PPI therapy may prevent neoplastic progression over time, significant regression of Barrett's mucosa length has not been demonstrated.[29] Nevertheless, based on the current literature it seems prudent to define PPI failure in patients with Barrett's oesophagus as those who lack sufficient symptom relief and complete healing of associated oesophageal inflammation while receiving PPI once daily.

The PPI failure phenomenon *per se* in patients with Barrett's oesophagus has been scarcely studied. Unfortunately, many studies already used high doses of PPIs in these patients as the initial therapeutic strategy. In one study, all BE patients receiving omeprazole 20 mg once daily were maintained symptom-free.[30] However, several studies using high dose of PPIs (omeprazole 80 mg, lansoprazole 60 mg and omeprazole 60 mg once daily) demonstrated complete heartburn resolution in 80–85% of the patients.[28, 31, 32]

POTENTIAL CAUSES FOR PPI FAILURE

Several factors have been postulated as possibly contributing to the continuation of GERD symptoms despite PPI therapy. Some are very important clinically, while others appear to be relatively uncommon and have only limited clinical value (Table 1). Additionally, it is not uncommon that more than one cause for PPI failure may be recognized in a subset of patients. It should also be emphasized that some of the proposed underlying mechanisms have demonstrated association with PPI failure but the extent of causality and the true nature of the relationship remain unknown.

COMPLIANCE

Prior to any further evaluation, all patients suspected of experiencing PPI failure should be assessed for

Table 1. Proposed underlying mechanisms for PPI failure

Reasons for PPI failure	Clinical significance
Compliance	High
Helicobacter pylori infection status	Low – dose adjustment is not necessary
Bioavailability	Low – response rates to the different PPIs are usually comparable
Nocturnal acid breakthrough	Low – a gastric physiological phenomenon with unclear clinical relevance
Rapid metabolism	Low – probably uncommon
PPI resistance	Low – paucity of data
Duodenogastro-oesophageal reflux	Unclear – association has been established, extent of causality unclear
Non-acidic gastro-oesophageal reflux	Unclear – association has been established, extent of causality is unclear
Delayed gastric emptying	High – in relevant cases with documented delayed gastric emptying
Visceral hypersensitivity	High – most PPI failure patients originate from the NERD phenotype
Psychological comorbidity and emotional stress	Unknown – no studies thus far

PPI, proton-pump inhibitor; NERD, non-erosive reflux disease.

compliance. Poor compliance is probably the single most common cause for reported PPI failure.

Several factors may contribute to patient's compliance when long-term treatment is prescribed. These factors include knowledge about the treated disorder and the prescribed drug, perceived severity of symptoms, side-effects, number of pills or additional medications, patient's age and personality[33] (see Table 2). Additionally, GERD is primarily a symptom-driven disease, where many patients continue to take medications as long as they experience symptoms. When symptoms resolve, patients commonly lose the drive to take their PPI leading to discontinuation of treatment. According to a large population-based survey, only 55% of the GERD patients took their PPI once daily for 4 weeks as prescribed. In contrast, 37% took their PPI during 12 days or less out of the month.[34]

Whilst patients may comply with once a day PPI therapy, many may not take the drug correctly. This is especially relevant to PPIs, because timing and frequency of dosing are critical for maximal efficacy. PPIs should be taken approximately half an hour before a meal. This is supported by a study[35] demonstrating a significantly better gastric acid control when omeprazole or lansoprazole were taken 15 min before breakfast, vs. without breakfast. Unfortunately, many patients are not aware of the need to take PPIs prior to a meal, commonly because of doctors' failure to provide proper instructions. Some patients may take their PPI at bedtime, again reducing the efficacy of the drug, by not consuming it prior to a meal.

An important clue for poor compliance is the recurrence of GERD-related symptoms after a period of complete symptom resolution. Unlike the case of H_2-blockers, tolerance to PPIs has not been documented.

Table 2. Factors that may adversely affect patients' compliance with PPI therapy

Knowledge about the treated disorder
Desire for personal control
The prescribed drug
Perceived severity of symptoms
Side-effects
Number of pills per day
Additional medications
Age
Personality
Socioeconomic status
Health care coverage

PPI, proton-pump inhibitor.

HELICOBACTER PYLORI INFECTION

It has been demonstrated that *Helicobacter pylori* infection improves the efficacy of acid inhibition by a PPI. Studies have shown that PPIs produce greater acid suppression in *H. pylori*-positive patients when compared with *H. pylori*-negative patients.[36] The suggested underlying mechanism is migration of *H. pylori* proximally in the stomach to the corpus or fundus during PPI treatment. These areas of the stomach contain parietal cells, which are responsible for acid production. However, long-term treatment with a PPI in *H. pylori*-infected patients may result in atrophic gastritis which may progress to intestinal metaplasia and dysplasia.[37]

Holtmann *et al.*[38] demonstrated that of all erosive oesophagitis patients that received 4 weeks of pantoprazole 40 mg once daily, 23.7% of the *H. pylori*-negative

patients failed healing of their oesophagitis when compared with 13.4% of the *H. pylori*-positive patients ($P = 0.0005$). Relief of GERD symptoms was also significantly ($P < 0.05$) higher in *H. pylori*-positive patients (84%) when compared with *H. pylori*-negative patients (78%). However, the prevalence of *H. pylori* infection has been rapidly decreasing in the United States and other developed countries resulting in a very low background prevalence that cannot explain the large percentage of PPI failure patients.

BIOAVAILABILITY

Oral bioavailability may differ significantly from one PPI to another, and may be decreased further when the drug is taken with food or antacids.[39] Bioavailability has been suggested as a contributory mechanism for PPI failure. For example, the bioavailability of omeprazole is about 30–40%, which is significantly lower than the 80% bioavailability of lansoprazole or pantoprazole. However, these pharmacokinetic properties appear to have limited clinical relevance. With some slight differences, all PPIs were repeatedly shown to have comparable clinical efficacy.[5, 40]

PPI RESISTANCE

A single abstract was published in 1995 investigating the possible role of specific mutations in the H^+/K^+-ATPase that might lead to PPI resistance.[41] Such contributory mutations were not found; however, and no further studies on specific genetic mutations causing PPI resistance are available in the literature.

RAPID METABOLISM

The 2C19 isoform of cytochrome p450 (CYP2C19) is the principal enzyme responsible for the metabolism of PPIs. Inherited genetic polymorphisms of this enzyme determines the plasma concentrations of these drugs, and hence their ability to suppress acid production. The relative impact of CYP2C19 pathway on the metabolism of PPIs has been reported to be mostly in omeprazole and esomeprazole followed by pantoprazole, lansoprazole and (the least affected) rabeprazole.[42]

Because the metabolites of PPIs are pharmacologically inactive, rapid metabolizers may potentially demonstrate lower efficacy of PPIs. In contrast, poor metabolizers may show increased efficacy due to increase in bioavailability of the drug. The expression of the poor metabolizer phenotype is most common in Asian subjects, and is relatively uncommon in Caucasians.[43] Up to fivefold higher exposure to omeprazole, pantoprazole and lansoprazole has been observed in poor metabolizers when compared with extensive metabolizers. A study by Furuta *et al.*[44] demonstrated 45.8% healing rates in extensive metabolizers with erosive oesophagitis treated with lansoprazole 30 mg daily for 8 weeks when compared to 84.6% in poor metabolizers with erosive oesophagitis. Furthermore, extensive metabolizers with severe erosive oesophagitis demonstrated a very low (16.7%) healing rate. Accordingly, poor metabolizers of lansoprazole had significantly higher blood levels of lansoprazole 3 h after taking the medication, and patients that were successfully treated had higher levels of lansoprazole than patients who failed therapy. Oesophageal healing rates of patients with erosive oesophagitis treated with lansoprazole 30 mg daily for homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers were 57%, 69%, and 73% in 4 weeks and 77%, 95% and 100% at 8 weeks, respectively.[45] No comment was made; however, on symptom relief among patients based on CYP2C19 genotype.

Recently, Egan *et al.*[46] studied the effect of CYP2C19 genotype on gastric acid secretion, oesophageal acid exposure and occurrence of symptoms in 60 patients with GERD while on PPI therapy. Whilst the variant alleles predicted gastric acid suppression there was no association between the CYP2C19 genotype and oesophageal acid exposure or reflux-related symptoms. The latter study and others suggest that in clinical practice determining CYP2C19 genotype will unlikely predict the clinical efficacy of a PPI. However, in a small group of patients with severe erosive oesophagitis, who are refractory to treatment, the possibility of extensive metabolism of PPI should be entertained.

NOCTURNAL ACID BREAKTHROUGH

Nocturnal acid breakthrough (NAB) has been arbitrarily defined as the presence of gastric pH below 4 for at least 1 h during the night – in patients on PPI therapy. This physiological phenomenon has been observed in 75% of all individuals (GERD patients as well as healthy subjects) taking PPI twice a day.[47] It has been hypothesized that NAB is the underlying pathophysiological mechanism responsible for refractory GERD. The

original study demonstrated the presence of NAB in subjects receiving PPI twice daily. However, correlation between this gastric phenomenon and patients reported GERD symptoms was not attempted.

The NAB was later suggested as a surrogate marker for PPI failure. Despite lack of any direct evidence that NAB is responsible for the continuation of symptoms in PPI failure patients, a therapeutic approach that included the addition of histamine-2 receptor antagonist (H_2RA) at bedtime was introduced and quickly adopted. However, despite the presence of NAB with all PPI regimens, oesophageal acid reflux (90%) and patients' symptoms (100%) are all well controlled.[48] Additional studies have shown that NAB events do not demonstrate a temporal relationship with reflux-related symptoms.[49] Furthermore, 71% of the patients with GERD who failed treatment with PPI twice daily,[50] experienced NAB, but only 36% had correlation between symptoms and NAB events. Moreover, there is no relationship between NAB and nocturnal heartburn.[51]

In summary, the presence of NAB in patients treated with a PPI is a physiological phenomenon that has yet to demonstrate an association with clinical parameters, such as symptoms or erosive oesophagitis. Presently, there is no clinical evidence that NAB should be ruled out in patients who failed PPI treatment.

DUODENOGASTRO-OESOPHAGEAL REFLUX

Duodenogastro-oesophageal reflux (DGER) is the reflux of duodenal contents through the stomach and into the oesophagus.[52] This physiological event has been implicated as a possible cause for heartburn symptoms in patients that are unresponsive to PPI therapy.

It has been proposed that bilirubin concentration in the refluxate is an adequate tracer for DGER.[53] The fiberoptic spectrophotometric probe Bilitec 2000 is used for the assessment of bilirubin level in oesophageal refluxate. Several studies demonstrated a close correlation between DGER and severity of GERD. Vaezi and Richter[54] have shown DGER in 95% of patients with Barrett's oesophagus, 79% of those with erosive oesophagitis and only in 50% of the patients with NERD. Furthermore, aggressive acid suppression with PPIs dramatically decreased both acid and DGER,[55, 56] perhaps by decreasing the volume of gastric contents.

In a recently published study, Tack *et al.*[57] suggested that DGER is an important underlying mechanism in GERD patients who are poorly responsive to PPI. The authors showed that DGER was significantly more common (64%) than acid reflux (37%) in patients who continued to have GERD-related symptoms on either standard dose or double-dose PPI. Patients with erosive oesophagitis experienced a higher number of DGER episodes (35 vs. 15.5) and longer exposure time to DGER (11.9% vs. 6.3%) when compared with NERD patients. Whilst the results are very intriguing, the study failed to demonstrate that DGER is the direct cause of patients' persistent symptoms on PPI therapy.

Overall, there is evidence for an association between DGER and PPI failure, but the extent of causality remains to be elucidated. This is compounded by the usage of a technique that relies on a surrogate marker (bilirubin) for assessment of bile reflux. It is still unclear what components if any in the DGER might cause persistent heartburn symptoms.

NON-ACIDIC GASTRO-OESOPHAGEAL REFLUX

Non-acidic gastro-oesophageal reflux is the reflux of gastric contents into the oesophagus with pH > 4. The recent introduction and usage of the multichannel intraluminal impedance (MII) with pH sensor allowed the detection of reflux of gastric contents into the oesophagus without concomitant drop in pH below 4. This recording assembly can disclose the characteristics of the gastric refluxate (gas, liquid, mixed gas and liquid). By using the MII with pH sensor, Vela *et al.*[58] demonstrated a shift in the reflux characteristics in patients who failed PPI twice daily. Whilst there was no difference in the number of reflux events on PPI therapy when compared with baseline, most of the reflux events detected were non-acidic. The authors suggested that non-acidic reflux was associated with classic GERD symptoms, although less so than acidic reflux. Additionally, symptoms such as regurgitation, sour or bitter taste in the mouth were more associated with non-acidic reflux than heartburn. Shay *et al.*[59] evaluated 29 patients who were symptomatic despite twice daily PPI therapy, using the MII-pH test. Of the 22 patients with study day symptoms, 41% had an abnormal MII but successful acid suppression and positive symptom index (SI) with non-acidic GER. Regurgitation was the most common reported symptom (71%). Additionally, 18% had both failed acid suppression and abnormal MII parameters, with symptoms more associated with acidic rather than non-acidic reflux. The other 41% had both

successful acid suppression and normal MII parameters. All those without symptoms during the study day had a normal MII. This study suggests that non-acidic reflux is associated with symptoms in the minority of patients who failed PPI therapy.

The role of non-acidic reflux, let alone its composition, in PPI failure remains to be elucidated. As with DGER there is evidence for association but the extent of causality is unknown. It is also unclear the level of overlap between non-acidic reflux and DGER.

VISCERAL HYPERSENSITIVITY

As was previously mentioned, NERD contributes most of those who fail PPI. Many of these patients originate from the functional heartburn subgroup, which accounts for up to 50% of the NERD patients.

Frazzoni *et al*. have recently evaluated patients with different phenotypic presentations of GERD (NERD, erosive oesophagitis and complicated GERD) and compared them to patients with functional heartburn and normal controls.[60] Patients with functional heartburn did not differ in distal oesophageal acid exposure profile, prevalence of hiatal hernia, distal oesophageal amplitude contractions and lower oesophageal sphincter (LES) basal pressure from normal controls. This study further demonstrates that mechanisms other than reflux are likely to play an important role in symptom generation of those with functional heartburn. Martinez *et al*. demonstrated that patients with NERD and abnormal pH test were more likely to demonstrate a SI >75% than functional heartburn patients (61.9% vs. 10.5%, $P = 0.0001$).[17] In the functional heartburn group, those with a negative SI reported having heartburn at pH < 4 only 12.7% of the time compared with 70.7% of the time in those with a positive SI, despite a similar mean number of heartburn episodes. Consequently, the authors proposed that most (63%) of the patients with functional heartburn appear to have heartburn symptoms unrelated to acid reflux. However, the authors also suggested the presence of a subgroup of patients that falls under the category of functional heartburn and demonstrate a close relationship between their heartburn symptoms and acid reflux events. Further support for this subgroup of patients derives from a therapeutic study in patients with functional heartburn using twice a day PPI.[18] In this study, the authors demonstrated that the partial response to PPI therapy seen in patients with functional heartburn is likely due to the subgroup of patients who demonstrate a close correlation between their symptoms and acid reflux events.

Thus far, the mechanisms for pain in patients with functional heartburn appear to be diverse and acid exposure within the physiological range is the underlying cause in only subset of patients. However, repeated studies in patients with functional heartburn, using either oesophageal balloon distension or electrical stimulation have consistently demonstrated a lower perception threshold for pain when compared to patients with other presentations of GERD.[25, 61] Furthermore, objective neurophysiological measures of oesophageal evoked potentials latency revealed that functional heartburn patients achieve equivalent latency and amplitude oesophageal evoked potential responses with reduced afferent input, suggesting heightened oesophageal sensitivity.[62] In contrast, stimulus response functions to acid in patients with functional heartburn demonstrated a more mixed response, which resulted in higher mean value for time to heartburn symptom and lower mean values for intensity and acid perfusion sensitivity score when compared to patients with NERD and abnormal pH testing. A quarter of the patients had a negative acid perfusion test. The latter study further supports the hypothesis that functional heartburn is composed from a heterogeneous group of patients. However, a significant subset of these patients is unlikely to have GER as the underlying stimulus for their heartburn. Further research is needed to explore the different mechanisms for symptoms in patients with functional heartburn, including the possibility of small changes in the oesophageal pH that do not traverse pH 4.0 (the arbitrary definition for acid reflux event). It is unlikely that oesophageal symptoms are generated only if pH drops below 4.0. Additionally, there is emerging data suggesting that even minute changes in oesophageal pH are sufficient to trigger heartburn symptoms in subset of patients with GERD.

GASTRIC EMPTYING

Delayed gastric emptying is often viewed as a significant contributing factor to the pathophysiology of GERD.[63] Several studies demonstrated that the prevalence of delayed gastric emptying in patients with GERD is approximately 40%.[64, 65] Some investigators have postulated that delayed gastric emptying may

contribute to PPI failure in GERD patients. Kudara *et al.*[66] evaluated gastric emptying in 15 patients with erosive oesophagitis who received lansoprazole 30 mg once daily for 8 weeks. Four of the patients who experienced persistent reflux symptoms and erosive oesophagitis demonstrated significant delayed gastric emptying when compared with the other 11 patients who had improvement in GERD symptoms and oesophageal inflammation.

Thus far, there is very little data about the frequency of delayed gastric emptying in patients who failed PPI therapy. It is known that patients with diseases that cause delayed gastric emptying do not demonstrate a higher prevalence of erosive oesophagitis.[67] Additionally, there is no correlation between delayed gastric emptying and response to PPI therapy.[68]

Regardless, the extent and the role of delayed gastric emptying in patients who failed PPI treatment remained to be further elucidated. It is possible that patients may continue to report dyspeptic type of symptoms while receiving PPI therapy. These symptoms may be confused and related to PPI failure.

PSYCHOLOGICAL COMORBIDITY

Other factors that may lead to PPI failure, such as psychological comorbidity, emotional status and stress have never been assessed. These factors appear to play an important role in patient's adherence as well as response to therapy.

DIAGNOSTIC TESTING

Several diagnostic modalities are available to evaluate patients who failed PPI therapy. They include upper endoscopy, ambulatory 24-h oesophageal pH monitoring, Bilitec 2000 and MII with a pH sensor.

Upper endoscopy

The value of upper endoscopy in patients who failed PPI therapy has been scarcely studied. Whilst commonly performed in practice, regardless if alarm symptoms are present or absent, the yield of the upper endoscopy in patients who failed PPI is likely very low. The presence of erosions in these patients may suggest, high grading of oesophageal inflammation prior to treatment, poor compliance, usage of pills that can damage the oesophageal mucosa or alcohol abuse.

Most erosive oesophagitis patients (≈90%) on PPI once a day given over a period of 8 weeks are expected to have normal oesophageal mucosa on repeated endoscopy at the conclusion of treatment. A subset of patients with high grading of erosive oesophagitis may not fully heal on a PPI once a day. Because patients with advanced grading of erosive oesophagitis (Los Angeles grades C and D) account for only 15–30% of the patients with erosive oesophagitis, their impact on the overall failure rate of patients with erosive oesophagitis is relatively small. Thus, only a very small percentage of erosive oesophagitis patients may require higher doses to maintain healed oesophageal mucosa.[69]

In a retrospective review, Loftus *et al.* found that 20% of the PPI-treated (unknown dosing) GERD patients had erosive oesophagitis on upper endoscopy.[70] Because of the retrospective nature of the study and other shortcomings, the implications of the study results about the role of upper endoscopy in PPI failure remain unknown.

pH testing

Ambulatory 24-h oesophageal pH monitoring has been widely used in evaluating patients with GERD for the presence of abnormal distal oesophageal acid exposure. The American Gastroenterological Association practice guidelines for the usage of pH testing suggested that the test should be considered in patients who failed PPI therapy and performed while patients were on treatment to ensure normalization of oesophageal acid exposure.[71]

Several studies assessed the value of pH testing in the context of PPI failure. In one study, 61.4% of the GERD subjects undergoing pH testing for persistent symptoms while receiving standard dose PPI once a day, had a normal test.[72] There was no correlation between a negative pH test and age, gender or brand of PPI. In a recent study, 69% and 96% of the GERD subjects with refractory symptoms who underwent pH testing on PPI once daily or PPI twice daily, respectively, had a normal test.[73] Cost analysis revealed overall expenditure of $125 000 per typical GERD symptom with no additional diagnostic yield (Figure 3).

Increasing the duration of acid exposure evaluation to 48 h by the Bravo wireless pH capsule has been suggested to improve the sensitivity of the pH test.[74] It allows evaluation of patients who demonstrate normal acid exposure during day 1 of pH evaluation and abnormal oesophageal acid exposure during day 2.

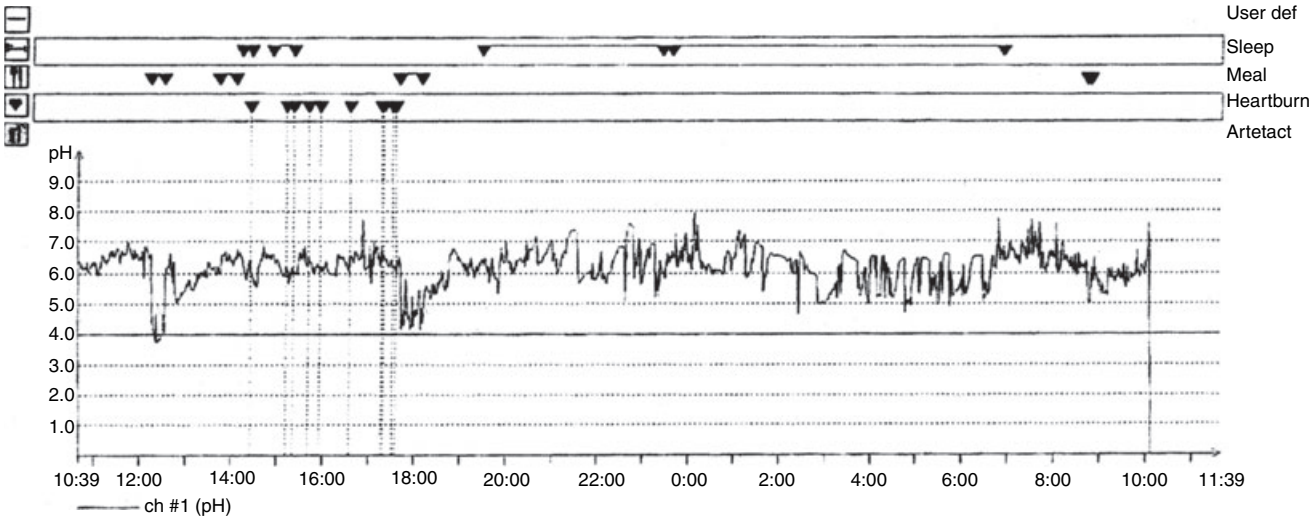

Figure 3. A 24-h oesophageal pH tracing in a patient who continued to be symptomatic on proton-pump inhibitor twice a day. The pH test was unrevealing despite repeated reports of heartburn symptoms by the patient implying that symptoms were probably not caused by acid reflux.

However, the value of the wireless pH capsule in evaluating patients who failed PPI remained to be elucidated.

Overall, pH testing is commonly used in clinical practice to evaluate patients who failed PPI therapy.[75] However, the value of this diagnostic technique appears to be very limited in patients who failed PPI once daily and non-contributory in those who failed PPI twice daily.

Bilitec 2000

Bilitec 2000 is an ambulatory system consisting of a fiberoptic probe which detects bilirubin based on its spectrophotometric properties with a peak absorption of 450 nm.[76] The probe is passed transnasally into the oesophagus and is connected to a data logger device. The Bilitec was developed to assess bile reflux using bilirubin as a surrogate marker. However, because the technique lacks the capability of directly detecting bile, investigators elected to use the term DGER, which encompasses different components of duodenal content (bile, pancreatic juice and enzyme as well as others). The value of this technique in clinical practice remained very limited. As mentioned previously, a recent study of a small number of patients suggested that by adding Bilitec to pH monitoring, documentation of persistent reflux increased from 37 to 75%.[57] This study has raised general interest in the technique as a useful assessment tool of patients who failed PPI therapy. However, more studies are needed to demonstrate that Bilitec 2000 is helpful in evaluating PPI failure patients and tailor proper therapy.

Multichannel intraluminal impedance

Multichannel intraluminal impedance has been introduced as a new technique for assessing oesophageal function and composition of food boluses as well as GER. The addition of a pH sensor helps to determine if the refluxate is acidic or non-acidic.

As was already mentioned, MII has been suggested to be an important modality for evaluating patients who failed PPI therapy.[58] However, the technique lacks standardization, uses parameters that were arbitrarily determined and the pH sensor has been considered as 100% sensitive to acid reflux. Furthermore, documenting non-acidic reflux in patients who failed PPI suggests association, but not necessarily causality. The exact clinical role of MII in oesophageal disorders and specifically in PPI failure requires further evaluation.

TREATMENT

The proper therapeutic approach that patients who failed PPI once daily should receive is not well

established in the literature. The commonly used approach, which has become the standard of care in clinical practice, is doubling the PPI dose. Hetzel *et al.* compared the healing effect of omeprazole 20 mg once daily vs. 40 mg once daily in patients with erosive oesophagitis over a period of 8 weeks. The authors demonstrated that by doubling the PPI dose oesophageal healing has improved by only 6%.[77] Interestingly, treatment for an additional 4 weeks resulted in further improvement in oesophageal healing, albeit very limited. The extent of symptom improvement is not reported in this study but the authors noticed that patients receiving omeprazole 40 mg once daily had a small advantage over those who received omeprazole 20 mg once daily. Whilst this study was not specifically intended to assess therapy for patients who failed PPI, it does provide us with clues about the benefit of doubling the PPI dose. In a study that did not attempt to specifically evaluate PPI failure patients, the authors assessed if omeprazole 40 mg daily offers additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis.[78] During the additional 4 weeks of treatment, patients receiving omeprazole 40 mg daily demonstrated higher healing rates (64% vs. 45%, $P < 0.02$) and reports of heartburn relief (72% vs. 60%, $P < 0.002$). Another study demonstrated that complete resolution of symptoms is achieved by only 22–26% of uninvestigated GERD patients who required double-dose PPI.[5] The latter study clearly suggests that most of the patients who failed PPI once a day will continue to be symptomatic on PPI twice daily. Other investigators have looked at symptom improvement rather than the hard to achieve clinical outcome – complete symptom control. In fact, some have even suggested that those who failed PPI therapy may be content with sufficient control of heartburn symptoms, allowing patients the experience of a few heartburn episodes per week.[12]

Doubling the PPI dose appears to be also beneficial in patients with functional heartburn, who are likely to generate many of the PPI failure patients. Watson *et al.* performed a double-blind, crossover, placebo-controlled trial of omeprazole 20 mg twice daily over 4 weeks in the treatment of patients with functional heartburn.[18] The drug improved symptoms in 61% of subjects. As expected, almost all responders also had a positive correlation between their symptoms and acid reflux events. This study, although lacking long-term follow-up, further cements the notion that the hypersensitive oesophagus subgroup within the functional heartburn group will likely respond to higher doses of PPI. It has yet to be elucidated how high one can raise the PPI dose and still improve symptoms or increase the number of complete responders.

Knowing that most GERD patients who continued to be symptomatic on PPI twice a day have a normal oesophageal acid exposure,[73] it is highly unlikely that increasing the PPI dose to three times daily or even higher will provide any significant additional benefit to patients.

For GERD patients who are still not controlled on PPI twice daily, there is very little information in the literature about potential therapeutic directions. In GERD patients with symptoms such as, regurgitation, sour or bitter taste in mouth and evidence of non-acidic reflux or DGER while on PPI twice daily, the addition of a transient lower oesophageal sphincter relaxation (TLESR) reducer has been suggested to be useful. In one study, the addition of baclofen (20 mg three times daily), a γ-aminobutyric acid (GABA)-B receptor agonist with inhibitory effect on TLESR, to a PPI once daily significantly reduced DGER exposure and DGER-related symptoms when compared with baseline.[79] Whilst the latter study supports the usage of baclofen in clinical practice, anecdotal experience with the drug in PPI failure patients has not been rewarding. Additionally, baclofen may result in a variety of side-effects, such as confusion, dizziness, light-headedness, drowsiness, weakness and trembling. Tegaserod, a partial $5HT_4$ agonist has been shown to have some limited effect on TLESR.[80] It has yet to be determined in a placebo-controlled trial, if adding tegaserod to patients who failed PPI once daily is an effective therapeutic strategy. Unfortunately, we are currently devoid of other TLESR reducers and thus limited to the agents mentioned above. The role of adding a promotility drug in patients who failed PPI once a day is unknown. However, in patients with PPI failure who demonstrate delayed gastric emptying, adding a promotility drug is an attractive option. It is unclear, however, if adding a promotility agent to those who lack evidence of delayed gastric emptying is a beneficial therapeutic modality.

Adding a pain modulator in PPI failure patients is another attractive therapeutic strategy, because of the notion that many patients who fail PPI are likely to have functional heartburn. Pain modulators, such as tricyclics and selective serotonin reuptake inhibitors (SSRI), have been shown to be highly efficacious in

patients with non-cardiac chest pain of presumed oesophageal origin.[81–83] These visceral analgesics are used in non-mood altering low doses, to relieve oesophageal pain. Presently, there are no studies to demonstrate their value in PPI failure patients, but they may provide a therapeutic alternative until more novel and GI-specific pain modulators are available. Adding a pain modulator to a PPI, or just providing a pain modulator alone to those without any improvement on a PPI are the different therapeutic strategies that can be entertained in PPI failure patients.

The role of adding bile acid binders, such as cholestyramine in PPI failure patient is yet to be elucidated. There is still controversy if these therapeutic modalities should even be considered in GERD.

The use of antireflux surgery in patients who failed PPI has been discouraged because of the evidence that positive response to medical therapy is predictive of surgical success.[84] For patients who failed PPI because of symptoms suggestive of volume reflux, such as regurgitation, sour/bitter taste in the mouth, surgery may be an effective modality. However, studies to support such therapeutic intervention are still lacking. Similarly, the usage of one of the endoscopic techniques to treat GERD in patients who failed PPI has been suggested. Several studies have reported that these endoscopic techniques may reduce or eliminate PPI consumption in patients who demonstrate only partial response to PPI therapy.[85–87] Regardless, the role of endoscopic therapy in GERD has been under close scrutiny in last few years, because of untoward adverse effects and evidence of improvement of subjective parameters only, when compared with sham intervention. Further studies are needed to assess the role of endoscopic therapy in GERD in general and specifically in PPI failure patients.

In conclusion, GERD patients who failed PPI once daily will benefit from doubling the PPI dose. If patients continued to be symptomatic on twice daily PPI, either diagnostic evaluation with MII + pH sensor and Bilitech 2000 or further treatment could be entertained. Both diagnostic techniques are not readily available, invasive, costly and somewhat labour intensive. Consequently, in patients with regurgitation and/or sour/bitter taste in mouth, baclofen, tegaserod and potentially antireflux surgery may provide symptom improvement. In those with clear evidence of delayed gastric emptying, adding a promotility drug could be considered. The rest of the patients should be evaluated for the possible addition of a pain modulator (see Figure 4).

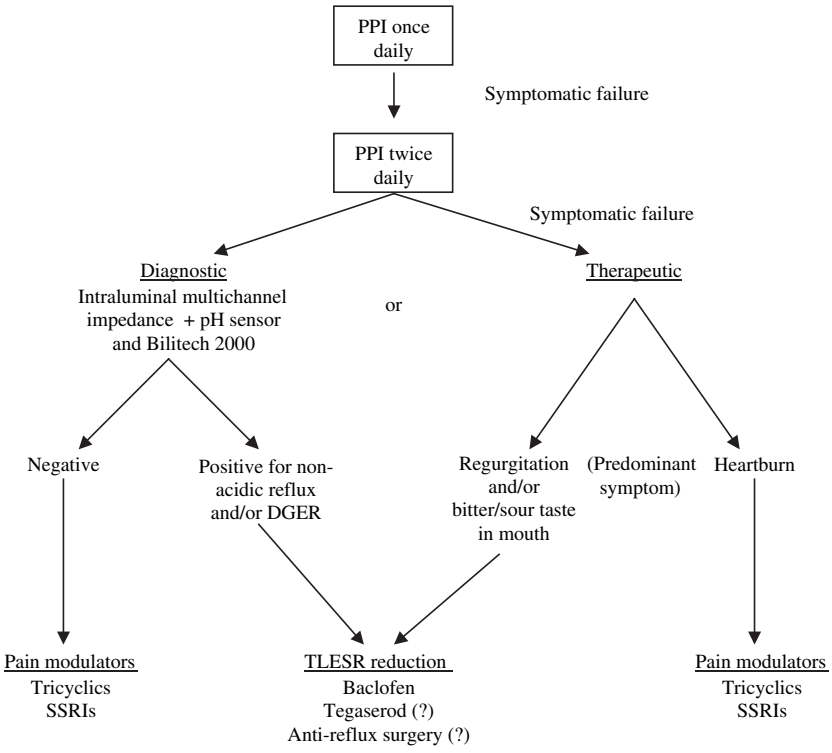

Figure 4. Therapeutic algorithm of gastro-oesophageal reflux disease (GERD) patients who failed proton-pump inhibitor (PPI; not including patients with Barrett's oesophagus).

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