

Title: The tapestry of reflux syndromes: translating new insight into clinical practice

Running Head: Management of uninvestigated reflux symptoms

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Introduction

For decades, the rationale for treatment of gastro-oesophageal reflux disease (GORD) with acid suppressors, such as proton pump inhibitors (PPIs), was that symptoms were attributable to reflux of acidic stomach contents into the oesophagus. However, recent advances in the understanding of how brain-gut interactions can modulate the perception of visceral stimuli have complicated the concept of GORD.¹ It is increasingly evident that altered perception of reflux is an important underlying cause of symptoms.² A number of syndromes related to visceral hypersensitivity and central nervous system dysregulation are now recognized as “functional” gastrointestinal (GI) disorders, potentially localised to the oesophagus,³ bowel, stomach, duodenum, anorectum, gallbladder, or multiple GI sites in the same patient. These functional syndromes are common; an internet-based health survey of almost 6,000 adults in the US, Canada, and the UK found that 35% had symptoms compatible with some functional GI disorder and 7% met diagnostic criteria for a functional oesophageal disorder.⁴ This could potentially account for a large fraction of the adults with weekly reflux symptoms in population-based assessments (global prevalence ~13%).⁵ However, it being impractical to investigate all of these patients, the recognition of altered perception as a major determinant of reflux symptoms has had little impact on management in general practice.

To provide guidance for the management of uninvestigated reflux symptoms in primary care, a series of sponsored (RB Healthcare Ltd., UK) workshops were held among gastroenterologists, GI surgeons and general practitioners. The objective was to translate recent research findings into clinical practice strategies.

Reflux symptom prevalence is increasing, but is GORD?

Epidemiological data suggest that the prevalence of GORD has increased considerably since the mid 1990s. However, wider public awareness of the link between reflux symptoms and oesophageal cancer⁶ has likely contributed to the increased presentation of symptomatic patients in primary care. Additionally, the more we understand the multifaceted pathophysiology of reflux symptoms, the more it becomes clear that the Montreal Definition (*“a condition that develops when the reflux of stomach contents into the oesophagus causes troublesome symptoms and/or complications”*) is oversimplified in not accounting for functional GI syndromes (visceral hypersensitivity and central nervous system dysregulation).

Most patients with reflux symptoms (~65%) do not have erosive oesophagitis on upper endoscopy⁷ and form a heterogeneous group of patients. When subtyped using prolonged ambulatory oesophageal pH-metry, patients without erosive oesophagitis can be subcategorized as having one of three syndromes; (1) nonerosive reflux disease (NERD, ~40%), wherein oesophageal acid exposure is quantifiably abnormal, (2) reflux hypersensitivity (~35%), wherein oesophageal acid exposure is quantifiably normal but symptoms are associated with reflux events, or (3) functional heartburn (~25%), wherein acid exposure is quantifiably normal and perceived symptoms are unrelated to reflux events.⁷ Thus, while the association between acidic gastro-oesophageal reflux, symptoms, and oesophagitis is sometimes beyond doubt, the expansive definition of GORD to include scenarios in which symptoms are only “potentially” attributable to acid or reflux is problematic for the clinician.^{1, 2}

Overutilisation of acid inhibition

PPIs are effective for treating and maintaining healing of oesophagitis and their widespread use has made high-grade oesophagitis and oesophageal peptic strictures relatively uncommon. The link between GORD and oesophageal adenocarcinoma is likely mediated through inflammation (oesophagitis), metaplasia (Barrett’s oesophagus) and dysplasia. However, PPI use might not decrease cancer risk and, compared with healing oesophagitis, they are less effective in resolving reflux symptoms. Persistent reflux symptoms are reported by up to 45% of PPI-treated patients in primary care and community studies.⁸ Nevertheless, PPI prescribing continues to increase globally and numerous studies report prescription of high-dose PPIs, without demonstrable improvement in symptoms, and perpetual PPI use in patients testing negative for gastro-oesophageal reflux. Furthermore, evidence suggests a systematic bias away from diagnosing functional GI disorder in favour of GORD.⁹

Unease regarding the unnecessary risks and costs associated with overutilisation of PPIs has led to deprescribing initiatives. However, efforts to prevent PPI overuse are hindered by lack of guidance on alternative therapeutic approaches and, perhaps, lack of confidence among primary care clinicians to attribute uninvestigated symptoms to a functional condition.

A detailed clinical history can help direct management

Early identification of patients whose symptoms are less likely to respond to acid inhibition can change the narrative for patient counselling and support. To achieve this, we can take a page from irritable bowel syndrome (IBS) management; a functional condition wherein diagnostic and therapeutic approaches are based on a detailed history rather than routine testing to exclude alternative aetiologies.¹⁰ Similarly, endoscopy is not required in patients presenting with reflux symptoms, unless alarm symptoms are present (outlined in regional

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guidelines, usually including dysphagia, food impaction, bleeding, unintentional weight loss). A thoughtful clinical history, taking a broad view of the patient's health and symptoms, could identify clinical characteristics indicative of functional oesophageal syndromes, which often overlap other functional symptoms and psychological factors. Once the clinical history points toward altered perception, the most relevant modulating factors can be addressed to improve management (see **Figure 1**).

Co-existing functional dyspepsia (nausea, early satiety, postprandial fullness, bloating), and IBS are observed more frequently in patients with functional heartburn than with oesophagitis or NERD, as are anxiety, depression, somatisation, and insomnia. Furthermore, a somatic symptom scale, i.e. the PHQ-12, can be useful to quickly identify signs of visceral hypersensitivity, such as backache, limb pain, palpitations or breathlessness.¹¹ On the other hand, gender, age, central obesity and lifestyle factors are important risk factors for acid-related syndromes (**Figure 1**). Reflux oesophagitis is found significantly more commonly on endoscopy in men than women ($15.9 \pm 2.5\%$ versus $6.1 \pm 1.6\%$, respectively; $P < 0.01$ ¹²) and, while older age is associated with more severe oesophagitis, functional heartburn has an inverse relationship with age.¹³

Patient counselling

A patient-centred approach is critical to elicit the motivation for consultation and the patient's worries about their symptoms. Cultural and language differences might be obstacles and patients should be encouraged to describe symptoms in their own words rather than assigning them "best fit" medical terms. Anxiety about upper GI symptoms, rather than the frequency or severity of the symptoms themselves, often motivates consultation; reassurance is sometimes the most important aspect of management. Helping patients appreciate the balance between altered physiology and perception may promote engagement and acceptance of treatment advice. However, the concept of 'acid reflux' as a cause of upper GI symptoms is deep-rooted and there may be resistance to the suggestion that other factors, especially psychological ones, cause symptoms. It is important to introduce patients, at an early stage, to the concept of the mind-gut link and the possibility that their symptoms could be caused by heightened perception as well as gastro-oesophageal reflux. This is especially important for patients with concomitant IBS, dyspepsia and other symptoms of functional disorder, because they are less likely to respond to PPI therapy.^{14,15}

Approaches to management

Lifestyle factors

The advent of safe, readily available, and inexpensive acid inhibitors has largely sidelined modulation of lifestyle factors as a first-line approach to reflux management. In a UK study, less than a third (28%) of patients with heartburn or regurgitation were informed about lifestyle measures by their general practitioner.¹⁶ The situation is not helped by the lack of investigation of lifestyle interventions in controlled clinical studies. Nevertheless, it is sensible to provide lifestyle advice and help patients explore potential lifestyle changes. Central obesity is a strong risk factor for GORD and increases the risk of erosive oesophagitis, Barrett's oesophagus, and oesophageal adenocarcinoma. Weight loss, even in non-obese patients, is proven to reduce oesophageal acid exposure and weight reduction has been shown to resolve refractory symptoms and reduce long-term PPI use.¹⁷ Similarly, smoking cessation has been shown to reduce reflux symptoms in normal weight individuals.¹⁸

For nocturnal reflux symptoms, avoidance of late evening meals and head-of-the-bed elevation have demonstrated benefit. Evidence regarding specific dietary factors and reflux is generally sparse and conflicting. However, a recent prospective, primary care study showed that patients with reflux symptoms could identify at least one dietary trigger for their symptoms (e.g. spicy food, chocolate, tomato) and that eliminating this food reduced symptoms in the short-term.¹⁹ Furthermore, 45% of patients agreed to continue treatment with dietary intervention alone, rather than progress to pharmacological therapy.¹⁹

PPI response does not equate to a diagnosis of GORD

A short (4 to 8 week) course of PPI treatment is a pragmatic approach for patients presenting with reflux symptoms who are unsatisfied with lifestyle interventions and over-the-counter therapies. However, PPI response does not equate to a diagnosis of GORD as it was demonstrated in 51% of primary care patients with upper GI symptoms who tested negative for GORD.²⁰ Furthermore, functional heartburn has been diagnosed in about half of PPI non-responders and a fifth of PPI responders.²¹ Hence, PPI response is not a reliable diagnostic tool even though it can help guide management.

PPI deprescribing

Reflux symptoms may occur intermittently with varying intensity, often linked to dietary patterns or psychological stress. In such circumstances a short course of PPI treatment may suffice. Explaining the rationale for deprescribing can help patients accept the process. There are several deprescribing strategies, e.g., lowering the PPI dose from twice- to once-daily, halving the dose, taking every second day, on-demand use, or stopping the PPI and using antacids, alginates, or an H₂RA, as required. The strategy that is most acceptable to the patient is the one that should be used. Practical recommendations for when and how to

reduce or discontinue PPI are now available (Farrell et al. 2017²²) and a successful nurse-led PPI deprescribing programme in UK primary care has also recently been reported.²³

Non-PPI options for persistent symptoms

Efficacy in healing high-grade oesophagitis is the only aspect of reflux disease management in which escalating the potency of PPI therapy (higher dose, twice-daily dosing, or more potent drug) has a demonstrable therapeutic gain. In contrast, there is no therapeutic gain with increased PPI dosage in patients whose reflux symptoms are not responding to standard dose PPI.²⁴ Poor adherence in terms of PPI dosing and timing (before meals) may be an issue, but evidence suggests that the refractoriness rate in nonerosive disease is still about 20% after dose optimisation.¹⁴ In a study of such patients, NERD, reflux hypersensitivity, and functional heartburn constituted 32%, 42%, and 26% of the total, respectively.¹⁴ Repetitive endoscopy should be avoided in such patients.³ Rather, they should be reassured and offered treatments to address the underlying pathophysiology, such as mucosal protection, neuromodulators, and behavioral therapy (**Figure 1**).²⁵ Treatments to coat the oesophagus and strengthen the mucosa barrier include alginate and hyaluronic acid plus chondroitin sulphate.²⁶ These treatments may also help patients with breakthrough symptoms on PPI, or during PPI deprescribing when transient rebound symptoms may occur. Neuromodulator options include tricyclic antidepressants, selective serotonin receptor inhibitors, noradrenergic reuptake inhibitors, or gabapentinoids.³ These therapies may be beneficial for patients with functional heartburn and reflux hypersensitivity who often exhibit psychosocial distress and reduced health-related quality of life proportionate to their symptom severity (see Dickman et al. 2014²⁷ for details on specifics of drug selection and dosing). Alternative approaches such as cognitive behavioral therapy, advice on coping mechanisms, relaxation therapy, acupuncture, hypnotherapy and exercise are complementary approaches to neuromodulation in selected patients. At the other extreme, patients strongly suspected of having unresolved symptoms on PPI therapy that are related to uncontrolled reflux, should be referred for further investigation. They may require laparoscopic fundoplication to restore anti-reflux barrier function, which remains an effective treatment in appropriate patients.²⁵

Conclusion

Reflux symptoms (heartburn, regurgitation) may be caused by altered physiology, altered perception, or both, but current treatment algorithms generally focus only on altered physiology. Although a short course of a PPI remains a mainstay of management, it should

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be used in conjunction with a good clinical history to help direct long-term management, including deprescribing and non-pharmacological interventions. There is no demonstrable therapeutic gain to dose escalation of PPIs in patients with suspected functional syndromes whose reflux symptoms are not responding to a standard dose. These patients should instead be managed with a combination of non-PPI therapeutic approaches such as lifestyle modifications, neuromodulators, mucosal protection, reassurance and psychological support.

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Conflict of Interest:

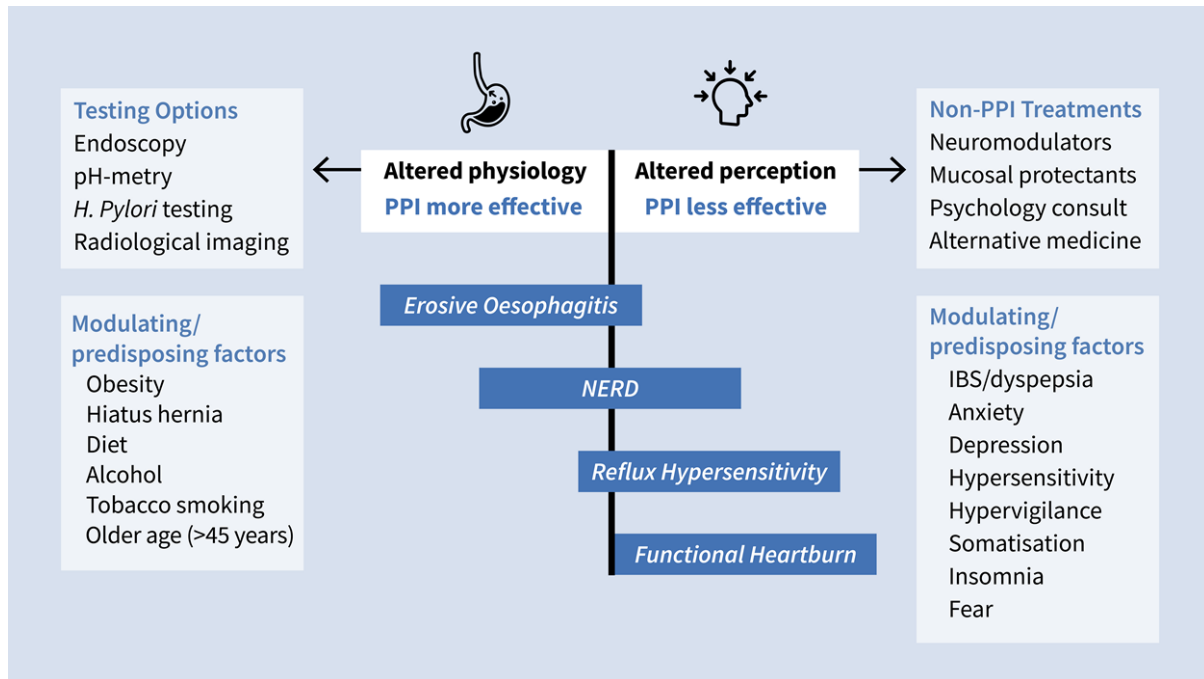
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FIGURES

BOX 1. Key points

- Reflux symptoms (heartburn, regurgitation) can be caused by altered physiology, altered perception, or a mixture of both. Current management algorithms for uninvestigated symptoms are not tailored to make this distinction.
- A detailed clinical history can help identify patients with acid-related or functional pathophysiology (visceral hypersensitivity or central nervous system dysregulation).
- Endoscopy, in the absence of alarm symptoms, is not likely to reveal organic disease or alter management.
- Responsiveness to a short course of PPI is not a reliable diagnostic tool for GORD but can be used with the clinical history to help direct long-term management and non-pharmacological interventions.
- Patients with suspected functional syndromes not responding to standard dose PPI should be managed with a combination of non-PPI approaches, such as lifestyle modifications, neuromodulators, mucosal protection, reassurance and psychological support.

Figure 1. Tailoring reflux symptom management to the suspected underlying pathophysiology. PPI response in conjunction with a detailed clinical history can help direct therapeutic interventions.



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