Expert speakers shared their experiences with delegates on how best to approach challenges both within primary care and at the interface with secondary care in a live full day interactive meeting.
The content was prepared and presented by the speakers and the views and opinions expressed were the speakers’ own, and do not represent the views and opinions of RB. Experts discussed practical suggestions on optimising endoscopy referrals, reviewing medication and re-assessing diagnoses. Difficult-to-manage cases were also presented to highlight the challenges that may be experienced when starting patients on proton pump inhibitors (PPIs) and following a complete, partial or lack of PPI response.

This report:
• highlights several of the key issues and challenges managing upper gastrointestinal (GI) conditions in primary care
• reviews several cases that highlight these challenges in clinical practice settings

**Key issues in management of upper GI conditions**

**The role of primary care**
In primary care, the management of upper GI conditions involves many skill sets: symptom assessment (including the identification of residual breakthrough, refractory or rebound symptoms); guiding patients on modifying lifestyle; developing a step-wise approach to therapy; and managing referrals for endoscopy or reflux testing. Although effective treatments are available for most upper GI conditions, significant challenges exist both within primary care and at the interface with secondary care.

**Clarifying nomenclature**
The clinical definitions used in upper GI management can be confusing. Gastro-oesophageal reflux disease (GORD) is a common, chronic condition in which gastric juices from the stomach flow up into the oesophagus. In addition to reduced quality of life, GORD can lead to Barrett’s oesophagus – an important risk factor for oesophageal adenocarcinoma. NICE guidelines currently cover symptoms of GORD as well as symptoms of dyspepsia. However, dyspepsia has no universally accepted definition and is not itself a diagnosis.

**Upper GI condition definitions**
- **Dyspepsia:** ‘a group of symptoms that alert doctors to consider disease of the upper GI tract’
- **Uninvestigated dyspepsia:** ‘has not been recently investigated by upper GI endoscopy’
- **Functional dyspepsia** (also called non-ulcer dyspepsia): dyspepsia of unknown cause
- **GORD:** ‘endoscopically determined oesophagitis or endoscopy-negative reflux disease’

The descriptions of upper GI symptoms can also be broad and ambiguous. Further discussion with patients about symptoms can reveal useful information when considering alternative diagnoses (discussed further in case study 4).

**The burden of increasing patient volume**
The number of patients presenting with upper GI symptoms places a substantial – and increasing – burden on healthcare systems, in terms of GP appointments, referrals for endoscopy and medication use. Dyspepsia has been reported to account for 1.2–4% of all primary care consultations in the UK. The resulting cost of medication (prescriptions for alginites, antacids, histamine receptor agonists and proton pump inhibitors) reached £161.9 million in 2015, second only to lipid-regulating drugs (£237.6 million). Although generic PPIs are now available, the number of PPI prescriptions is increasing exponentially. In 2012, omeprazole was prescribed 25.8 million times in England, increasing approximately 10% from the previous year. There is evidence of overprescribing of PPIs in the primary and secondary care setting in various countries, with estimates ranging from 13% to 65% of patients not having an appropriate indication for PPI therapy.

**Regularity of medication reviews**
NICE guidelines recommend annual reviews of patients who need long-term management of dyspepsia symptoms.

Many patients receive medication that can aggravate GORD, such as calcium antagonists, nitrates and bisphosphonates. It is also important...
to consider patients taking aspirin, steroids and anti-inflammatory drugs. These reviews also offer an opportunity to consider alternative diagnoses and step down or discontinue PPIs where appropriate.1

Over-burden of endoscopy services
Currently, there is a wide geographical variation in referral rates in patients with dyspepsia for endoscopy, and there has been an upward trend in the use of endoscopy over the past 10 years.1 This places pressure on endoscopy services, which is increasing following the publication of new cancer guidelines with lower thresholds for referrals1 in order to improve diagnosis of cancer. The 2015 Scoping for the future study estimated that an additional 750,000 endoscopies will need to be conducted annually by 2020 (representing a 44% increase on 2015 activity).10

Optimising endoscopy referrals
Given the pressure that endoscopy services are under, it is important to optimise the information that can be obtained. NICE guidance focuses on the exclusion of cancer and, therefore, does not address the causes of GI symptoms. While endoscopy for alarm symptoms is appropriate, the detection rate for cancer is relatively low.11 A proportion of referrals for endoscopy that focus on red flag symptoms for cancer (e.g. unexplained weight loss, GI bleeding or dysphagia) are, therefore, negative and provide no further information on the cause(s) of GI symptoms.

Endoscopies offer an opportunity to gain useful information about the tissue injury that occurs as a consequence of GORD, including Barrett’s oesophagus, as well as to investigate alternative diagnoses. It is important to remember that GI symptoms are not specific to any single upper GI condition. Some risk factors, such as hiatus hernia, can be detected by endoscopy.12

Addressing incomplete symptom control in a partial PPI response
Approximately 10–40% of patients taking standard-dose PPIs for GORD are estimated to have residual breakthrough symptoms,13 yet we currently lack comprehensive national guidance for GORD management when pharmacologic treatments are insufficient.7 Several factors should be considered when treating PPI-refractory GORD, including the PPI treatment itself (ie timing, regimen and adherence). In cases where the PPI is being taken as prescribed, a lack of complete response can occur for a number of reasons. These may be the result of the metabolism or PPI bioavailability in the patient, or due to weakly acidic reflux, duodenogastro-oesophageal reflux, residual acid reflux, delayed gastric emptying, oesophageal hypersensitivity, eosinophilic oesophagitis or concomitant functional bowel disorders.13 Treatment of refractory symptoms should aim to protect the oesophageal mucosa. Alginates have proven effective in reducing oesophageal acid exposure time14 and may be added to the regular PPI. Histamine receptor antagonists are sometimes recommended in patients with an inadequate response to a PPI,13 but the first adjustment should be to provide the PPI in a twice-daily dosage, if appropriate. Surgery may be considered in patients who do not wish to remain on medication for life.14 In addition, oesophageal sensitivity can be reduced with pain modulators or by assessing psychological comorbidity.11,13

Treating uninvestigated dyspepsia
NICE guidelines for the management of GORD and dyspepsia have remained relatively unchanged over the last decade, but a recent update on endoscopy referral from NICE 2014 is available.1 Patients with uninvestigated dyspepsia may be broadly divided into three groups to facilitate treatment selection: reflux-type (predominantly with heartburn and regurgitation); ulcer-type (with epigastric pain); and dysmotility-type (with nausea, bloating and fullness). Interventions for all three patient groups should include lifestyle advice and a stepwise approach to medication use, from antacids and alginates to PPIs. Patients with reflux-type dyspepsia should be offered a full-dose PPI for 4 weeks. In contrast, H. pylori should be tested for in patients with ulcer-type dyspepsia.3

Treatment of PPI-refractory GORD
• PPI13
  – Ensure correct timing and compliance
  – Twice-daily PPI if not already tried
• Mechanical factors13
  – Weight loss
• Protect oesophageal mucosa12,13
  – Alginates reduce oesophageal acid exposure time
• Reduce oesophageal sensitivity13
  – Pain modulators e.g. SSRIs (selective serotonin reuptake inhibitors)
  – Address psychological comorbidity
• Consider surgery13
  – Where symptoms are due to persistent reflux

When to refer for an opinion on management
• Patients with symptoms that are resistant or refractory to medical therapy
• Patients with an incomplete or total lack of response to a PPI despite typical symptoms
• When a patient specifically asks about anti-reflux surgery and is a suitable candidate
• When morbid obesity is present and the patient is a potential candidate for bariatric surgery
Case study 1:
When you suspect reflux (starting patients on a PPI)

In the first case example, a 35-year-old male office worker with a 2-month history of heartburn (mainly at night and after certain foods) was presented.

Discussion of this case began with the initial assessment, including identification of alarm symptoms (such as dysphagia, weight loss, nausea/vomiting or early fullness), any other dyspeptic symptoms (such as epigastric pain or bloating), treatments received for the symptoms, any precipitating medication, family history of peptic ulcers or upper GI cancer (despite being young), along with tobacco use, alcohol intake and diet.

Examining this case further, it was noted that the patient did not present with any alarm symptoms but had gained a stone since moving to an office-based job 6 months ago. The patient had no other dyspeptic symptoms. Symptoms were reduced by over-the-counter antacids and alginates but only in the short-term. The patient has no family history of reflux, smokes 10 cigarettes a day and drinks 21 units of alcohol a week (mainly at the weekend).

The discussion of how to treat this patient began with lifestyle advice (smoking, alcohol, weight management) followed by a stepwise approach to medication use, whether stepping up (antacids, alginates, then PPIs) or stepping down treatment. In this case of reflux-type dyspepsia, the patient should be offered a full-dose PPI for 4 weeks. Low doses are generally used for maintenance therapy and high doses for specific indications. If symptoms return, it is appropriate to use a low-dose PPI; alginates should be prescribed and used when stopping the PPI and for at least 2 weeks afterwards, then use as needed as the rebound hypersecretion settles. The discussion then turned to whether H. pylori should be tested for, the available tests and recommended treatments. The suitability of an endoscopy referral for this case was also discussed, with advice to follow NICE red flags for the diagnosis of cancer (see NICE guidelines).9

Case study 2:
When there’s still something going on (partial PPI responders)

In the second case, a 45-year-old Caucasian male presents with ‘indigestion’, which he has had for 10–15 years comprising on–off retrosternal burning and a bad taste in his mouth lasting 10 minutes at a time. The patient had frequent nausea but no vomiting and no dysphagia. His weight has increased (BMI = 30) and he has developed hypertension. He is an ex-smoker, consumes 30 units of alcohol a week and is otherwise healthy. He is prescribed standard-dose PPI therapy (omeprazole 20 mg OD). Upon follow-up review, it is noted that his symptoms of heartburn and regurgitation have improved but not resolved.

Discussion of this case began with diagnosis, which was considered most likely to be GORD. The suitability of an endoscopy referral was considered to be subjective. Although there is the option to treat empirically, it was considered best to rule out Barrett’s oesophagus first.

The patient was found to have a normal endoscopy. Unresolved symptoms such as those experienced by this patient, which are not fully responsive to a PPI, suggest PPI-refractory GORD. However, first it must be established whether the diagnosis is still reflux through careful examination of symptoms. Discussion of this case focused on various scenarios that may, or may not, be reflux, followed by the burden and treatment of PPI-refractory GORD (see ‘Treating recurrent upper GI symptoms’ above), and various mechanisms of PPI failure.

For patients such as this, it is important to confirm the presence of reflux for the diagnosis of PPI-refractory GORD. A 24-hour reflux study (using a pH sensor located just above the lower oesophageal sphincter) can differentiate complicated GORD from erosive reflux disease and other endoscopy-negative GI conditions, such as non-erosive reflux disease. Various other techniques, such as manometry and pH-impedance testing, can also differentiate PPI-refractory GORD from other indications. To manage patients who have shown some response to a PPI, the empirical use of add-on therapy such as alginates on top of PPI therapy can be appropriate. Alginates have proven effective in reducing oesophageal acid exposure time,10 and may be added to the regular PPI.
Controversies and issues in upper gastrointestinal management

Refractory symptoms: does it still mean reflux?

**Probably yes**
- Heartburn/regurgitation. PPI 20 mg once daily.
- Improves heartburn but bothersome regurgitation persists
- Heartburn/regurgitation. PPI 20 mg twice daily.
- Improves heartburn but bothersome regurgitation persists

**Heartburn/regurgitation. PPI 20 mg twice daily.**
- Heartburn persists

**Difficult to tell**
- Heartburn/regurgitation. PPI 20 mg once daily.
- Bad compliance, bad timing or intermittent intake of PPI. Heartburn/regurgitation persists

**Probably not**
- Heartburn and dyspepsia/irritable bowel syndrome (IBS) symptoms. PPI 20 mg once daily.
- Improves heartburn but dyspepsia/IBS symptoms persist
- Heartburn and hoarseness/cough/globus. PPI 20 mg once daily.
- Improves heartburn but hoarseness/cough/globus persists

Mechanisms of PPI-refractory symptoms

- Weakly acidic reflux
- Duodenogastro-oesophageal reflux
- Residual acid reflux
- Psychological comorbidity
- Oesophageal hypersensitivity
- Altered PPI pharmacokinetics
- Compliance or improper dosing time
- Delayed gastric emptying
- Concomitant functional bowel disorder

**Case study 3:**

**When it might be time to step down (management of the PPI responder)**

In the third case example, a 28-year-old female presented with heartburn that responded to treatment with PPI. Following 6 months of therapy and adherence to lifestyle advice, she remains PPI-dependent as symptoms return within days of stopping treatment.

Treatment with PPIs is expected to last 6–8 weeks, yet some patients receive PPIs for years. The discussion around this case reiterated the burden of long-term PPI prescriptions on the health system (see ‘The burden of increasing patient volume’ above) and the guidelines that recommend reducing PPI prescriptions through regular treatment reviews.

Despite treatment being effective in this case, there are several reasons to review therapy. NICE guidelines recommend treatment reviews to ensure patients receive the lowest PPI dose that controls symptoms effectively, to encourage on-demand use when appropriate and to return patients to self-management with antacids and/or alginites (unless there is an underlying condition or co-medication that requires continuing treatment).1

Rebound symptoms can be controlled with antacids or alginites.15

Medication may be discontinued by a pharmacist, nurse or doctor as long as there is an understanding of the original indication, and of the potential for indication-specific consequences of withdrawal and how these may be managed. A key barrier to stepping down or stepping off a PPI is rebound hyperacidity.

Studies conducted in primary care have shown the effectiveness of step-down using alginate therapy on-demand for symptomatic relief.16,17 During one study of 7,856 patients receiving PPIs in England, PPIs were successfully stepped down or stepped off in around 80% of 3,021 appropriate cases.16 In another study, 773 patients had their PPI treatment reviewed as part of a Polypharmacy Medications Optimisation Review.17 Of these patients, PPI treatment was stepped down in 22% and stepped off in 12%.17 In total, 329 medication prescriptions including PPIs were stopped over the 4-month review, leading to a total cost saving of £7,707 per annum (excluding review costs).17 If applied to all eligible PPI patients in that clinical commissioning group (CCG), the saving was estimated to be £46,951. At 12 months, secondary care referrals and endoscopies were reduced by 67% and 82%, respectively, totalling potential savings of £236,482 for the CCG.17

**Rebound hyperacidity can be a barrier to reducing PPI prescription**

- PPI withdrawal can cause rebound hyperacidity, which has the potential to lead to GORD symptoms.18
- Rebound hyperacidity is believed to be caused by increased gastric acid secretory capacity (which can increase by 50% after 3 months of PPI therapy), probably resulting from enterochromaffin-like (ECL) cell hyperplasia. ECL hyperplasia can lead to increased acid secretion.18

“During one study of 7,856 patients receiving PPIs in England, PPIs were successfully stepped down or stepped off in around 80% of 3,021 appropriate cases.”16
Case study 4: When it wasn’t reflux in the first place (PPI non-responder)

The discussion around the case of a PPI non-responder focused on the confirmation of diagnosis. Discussants referred to the recently published ROME IV guidelines, which recommend the diagnosis of potential underlying causes before making an assumption of functional heartburn, functional chest pain or functional dysphagia.19

Non-reflux causes of chest pain and/or dysphagia can be excluded by seeking a cardiology opinion to rule out cardiac disease, and an endoscopy with biopsy can rule out eosinophilic oesophagitis. When arranging an endoscopy for patients with PPI-refractory GORD, dysphagia or recurrent food bolus obstruction it is important to request a biopsy of the oesophagus to look for eosinophilic oesophagitis. The diagnosis and treatment of eosinophilic oesophagitis was reiterated during the discussion of this case.

Eosinophilic oesophagitis, where the oesophagus is infiltrated by eosinophils, has been increasingly recognised since it was first described in 1978.20 It is recommended that a biopsy be taken when eosinophilic oesophagitis is a diagnostic consideration,12 so it is important for these to be completed during the endoscopies. Eosinophilic oesophagitis can be treated with topical steroids and/or dietary changes, such as exclusion diets.21

The discussion of this case study included methodology and diagnostic benefits of techniques that may not be available at all centres. Examples include pH monitoring, which is a useful technique for detecting reflux events, and manometry, which can help diagnose oesophageal motor disorders such as achalasia, oesophageal junction outflow obstruction, diffuse spasm, jackhammer/hypermotile oesophagus and complete peristaltic failure.

The diagnosis of reflux hypersensitivity should include retrosternal symptoms including heartburn or chest pain, normal endoscopy, and the exclusion of eosinophilic oesophagitis and major oesophageal motor disorders. Referral to a gastroenterologist is recommended to confirm diagnosis through pH monitoring and positive symptom association.

Therapies for reflux hypersensitivity symptoms such as heartburn and indigestion include PPIs (if the patient is responsive), alginate antacids and pain modulators (tricyclic antidepressants, SSRIs and gabapentinoids).

The discussion of this case also highlighted various therapies that are available for non-reflux disorders. For example, the swallowing of air and belching associated with heartburn or regurgitation may be treated with physiotherapy, speech and language therapy or hypnotherapy. Also, dysmotility may be treated with medication (e.g. nitrates or calcium blockers), along with endoscopic or surgical interventions.

Elimination diets in the management of eosinophilic oesophagitis22

- Eosinophilic oesophagitis is an allergic disease driven by a dysfunctional immune response to food allergens. Symptoms vary by age and can include feeding aversion, food intolerance, vomiting, abdominal pain, dysphagia and food impaction

- Dietary approaches include:
  - An exclusive elemental diet with an amino acid-based complete liquid formulation; contains carbohydrates, fats, minerals, micronutrients and crystalline amino acids for protein
  - Elimination diets – allergy test-directed or empiric diets that exclude common disease-exacerbating foods. These diets offer patients more food choices, are more palatable, and have greater compliance, but the success rate is inferior to an elemental diet
  - There are not yet any published studies directly comparing the efficacy of the different approaches
References


