COMPASS Therapeutic Notes on the Management of Upper Gastrointestinal disorders

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Glossary of terms	
GI	Gastrointestinal
PPI	Proton pump inhibitor
H. pylori	*Helicobacter pylori*
HPA	Health Protection Agency
MHRA	Medicines and Healthcare products Regulatory Agency
Barrett's oesophagus	Replacement of normal distal squamous epithelial lining of the oesophagus by metaplastic columnar epithelium
Zollinger-Ellison syndrome	Small tumours (gastrinoma) in the pancreas or upper small intestine that produce gastrin, that leads to increased production of stomach acid.
GORD	Gastro-oesophageal reflux disease
H_2RA	Histamine-2 receptor antagonist
NNT	Number needed to treat
NSAIDs	Non-steroidal anti-inflammatory drugs
SOP	Standard operating procedure

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Dyspepsia
The British Society of Gastroenterology (BSG) defines dyspepsia as a group of symptoms that alert doctors to consider disease of the upper GI tract, and states that dyspepsia itself is not a diagnosis. Symptoms are typically present for at least four weeks and include upper abdominal pain or discomfort, heartburn, gastric reflux, nausea or vomiting.[1,2] The pathophysiology of dyspepsia depends on the underlying disease.[21] The most common causes of dyspepsia are gastro-oesophageal reflux disease (GORD), peptic ulcer disease and functional dyspepsia.[4] These will be discussed in this COMPASS Therapeutic Note.

Uninvestigated Dyspepsia

What is uninvestigated dyspepsia?
Uninvestigated dyspepsia refers to any symptoms of dyspepsia in a patient who has not received an endoscopy.

What is appropriate care for a patient with dyspeptic symptoms?
Given the complex interplay of causes, no single treatment approach provides consistent relief of dyspepsia symptoms. For the vast majority of patients, appropriate care means the management of symptoms with lifestyle advice and medication. For many patients, self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter (OTC)) and taken "as required" may continue to be appropriate for immediate symptom relief. However, additional therapy is appropriate to manage symptoms that persistently affect a patient's quality of life.[1] Even patients requiring long-term management of dyspepsia symptoms should be encouraged to reduce their use of prescribed medication stepwise; by using the lowest effective dose, by trying as-required use when appropriate, and by returning to self- treatment with antacid and/or alginate therapy.[1]

The role of the community pharmacist
Community pharmacists often provide the first point of contact for dyspepsia sufferers and can offer initial and ongoing help for people suffering from symptoms of dyspepsia.[1] This includes lifestyle changes, using OTC medication; help with prescribed drugs and advice about when to consult their GP.

Lifestyle advice
Patients presenting with symptoms of dyspepsia should be offered simple lifestyle advice, including advice on healthy eating, weight reduction and smoking cessation.[1] Identified precipitants of symptoms should be avoided. Common precipitants include smoking, alcohol, coffee, chocolate and fatty foods.[1] For patients with reflux symptoms, raising the head of the bed by 4 to 8 inches (by placing sturdy objects, such as wood, bricks, or concrete blocks, under it) and having a main meal 3 to 4 hours before going to bed may help.[1,5] Additional pillows should not be used as a

means to raise the head of the bed as this will only serve to compress the stomach.[1,5]
There can be an association between anxiety and dyspepsia symptoms. Therefore, discuss stress and anxiety levels and encourage relaxation strategies.[5]
Psychological therapies, e.g. cognitive behavioural therapy and psychotherapy, may improve symptoms in some individuals, at least in the short term.[1]

Medicines that can cause dyspepsia

Medicines should be reviewed for possible causes of dyspepsia.[1] **TABLE ONE** lists some medicines known to cause dyspepsia symptoms. If possible, medicines thought to be causing dyspepsia symptoms should be stopped. Where this is not clinically possible, gastro-protection with a PPI should be offered.[8]

TABLE ONE: Medicines that can cause dyspepsia symptoms[1,8] (list not exhaustive)

- NSAIDs
- Aspirin (including 75mg)
- Calcium antagonists
- Nitrates
- Theophyllines
- Bisphosphonates
- Corticosteroids
- Iron
- Antibiotics
- Slow release potassium
- Anticholinergic drugs (e.g. tricyclic antidepressants, drugs for urinary incontinence)
- Selective serotonin reuptake inhibitors (SSRIs)

Differential diagnosis

Other causes of epigastric pain should be considered, principally biliary and cardiac disease. Dyspepsia-related symptoms can be caused by:

- Cholelithiasis / cholecystitis
- Pancreatitis / pancreatic cancer
- Hepatobiliary disorders / malignancy
- Ischaemic heart disease.[8]

How is uninvestigated dyspepsia managed?

There is currently insufficient evidence to guide whether first line therapy should be empirical PPI for one month or a *H pylori* 'test and treat' approach in patients presenting with uncomplicated dyspepsia. Therefore, either strategy is an equal option.[1]

NICE Guidance – Uninvestigated Dyspepsia

- Patients presenting with dyspepsia for the first time (in the absence of red flags) can be managed in one of two ways:
  1. **Empirical full dose PPI therapy for 4 weeks OR**
  2. **'Test for and treat' for *H.pylori*.**[1]
- If symptoms recur after successful treatment, patients should be advised to step down PPI therapy to the lowest dose to control symptoms. 'As-needed' use of PPIs should also be discussed.[1]
- If there is an inadequate response to a PPI, a H_2 receptor antagonist (H_2RA) may be offered instead.[1]

What role for histamine receptor antagonists (H_2RAs) in uninvestigated dyspepsia?

PPIs are more effective in reducing dyspeptic symptoms than H_2RAs in trials of patients with uninvestigated dyspepsia. However individual patients may respond to H_2RA therapy.[1]

When to consider an endoscopy?

Endoscopy may be the only way to accurately determine the underlying cause of dyspepsia. However, it is not cost-effective to perform endoscopy in every patient, it places patients at a small risk of complication from the procedure, [21] and it is possible with a good clinical history to diagnose both GORD and functional dyspepsia without endoscopy in younger patients.[8]
In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms.[9] The chance of a dyspeptic patient under the age of 55 having gastric cancer is one in a million.[30] The harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer.[1] It should therefore be considered how endoscopy may change the patient's care management (if at all), especially in younger patients.

Red Flags / referral for endoscopy

- An urgent referral for endoscopy / a specialist with GI expertise should be made for patients of **any age** with dyspepsia who present with any of the following symptoms:
  - Chronic gastrointestinal bleeding
  - Dysphagia
  - Progressive unintentional weight loss
  - Persistent vomiting
  - Iron deficiency anaemia
  - Epigastric mass
  - Suspicious barium meal result
- In patients **aged ≥ 55 years** with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.[8,9]
- In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors:
  - Barrett's oesophagus
  - known dysplasia, atrophic gastritis or intestinal metaplasia
  - peptic ulcer surgery more than 20 years ago

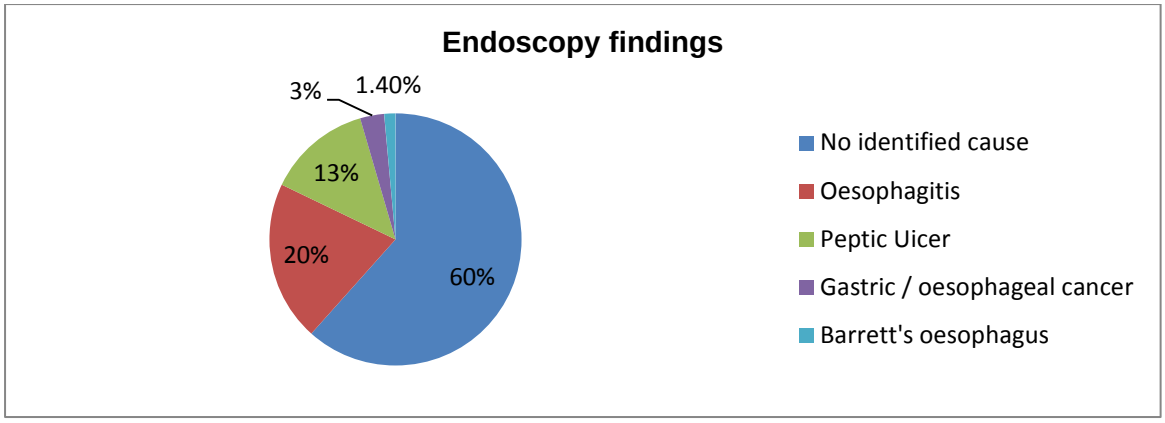
In the NICE referral guidelines for suspected cancer, the following timelines are recommended:

- **Immediate:** an acute admission or referral occurring within a few hours, or even more quickly if necessary
- **Urgent:** the patient is seen within the national target for urgent referrals (currently 2 weeks)
- **Non-urgent**: all other referrals.

Patients with dyspepsia plus significant acute GI bleeding should have **immediate** (**same day**) referral.[1]
Urgent referrals are to be seen **within two weeks**.[1]
This will include 'cancer access' or red flags.

Endoscopy findings

Of those undergoing endoscopy, the following is found:[1]



Proton Pump Inhibitors

Prescribing trends of PPIs

Some of the costs associated with treating dyspepsia are decreasing, with the introduction of generic PPIs. However, the overall use of PPIs is increasing.[1] Prescribing data for Northern Ireland show that 12% of the total population received a PPI in 2013.[3] Studies indicate that the numbers of people receiving long-term PPI therapy exceeds the prevalence of actual diseases in which a PPI is usually indicated.[16] That said, some of this will reflect long-term NSAID use and it is important that these patients receive gastro-protection with long-term PPIs.

When should PPIs be reviewed?

All newly initiated PPIs should be reviewed after four weeks.[8] Patients who require long term management of dyspepsia symptoms should be offered an annual review of their condition.[1]

How to step down PPIs?

Patients should be encouraged to consider a trial of stepping down or stopping treatment (unless there is an underlying condition or co-medication that needs continuing treatment – see later, 'Reasons to remain on a long term full dose PPI').[1]

Prescribed medication should be reduced in a stepwise manner:

1. Using the lowest effective dose
2. Trying 'as-needed' use when appropriate
3. Returning to self-treatment with antacid and/or alginate therapy.[1]

Antacids / alginates may be useful to be taken as required when patients are stepping down or stopping treatment with long-term PPI/acid suppression therapy. An SOP on stepping down PPIs is available on the HSCB Primary care intranet site: http://primarycare.hscni.net/PharmMM_Resources_Clinical%20Resources.htm#GI

'On demand' use of PPIs

'As needed' or intermittent use of PPIs may be considered, depending on patient preference.
'As needed': waiting for symptoms to develop before taking treatment. Once symptoms are relieved (often after a few days), treatment is stopped.
Intermittent use: a 2 to 4 week course of treatment when symptoms recur.[6]

Benefits to patients of reduced PPI therapy

To encourage stepping down of PPIs, the following points may be emphasised to patients:

- Fewer tablets to be taken
- Less risk of unwanted side effects.[10]

Safety concerns with long term use of PPIs

PPIs are generally well tolerated with a relatively low incidence of side effects during short term use. However, as PPIs become more widely used, evidence is starting to emerge about their long term safety concerns. Observational studies have shown an association between long term PPI use and uncommon side effects such as hypomagnesaemia, osteoporotic fracture, *Clostridium difficile* (*C. difficile*) infection, pneumonia, and vitamin B12 deficiency.[10] Theories for these adverse effects relate to the reduced acidity in the stomach – possibly causing reduced absorption of vitamins/minerals (hypomagnesaemia, osteoporotic fracture, vitamin B12 deficiency) and bacterial colonisation of the normally sterile upper GI tract (*C.difficile* infection and pneumonia).[10]

1. Hypomagnesaemia

Cases have been reported to the MHRA of hypomagnesaemia associated with long term PPI use (some cases occurred after 3 months of PPI therapy, but most occurred after 1 year of treatment). The MHRA has since advised that healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those who are taking digoxin or drugs that can also cause hypomagnesaemia e.g. diuretics.[11]

2. Osteoporotic fracture

There may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses and for long durations (>1 year). The MHRA issued advice that patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.[12]

3. *C. difficile*

The risk of acquiring *C. difficile* associated diarrhoea is two to three times higher in PPI users compared to non-users.[13] PPIs are usually stopped in patients following a *C difficile* infection. If restarted, the PPI should be withheld during future courses of broad spectrum antibiotics.[8]

Prescribing point – Magnesium levels
Magnesium levels should be measured in patients on long-term PPI (6 months or more) who are receiving digoxin and / or a diuretic.

Prescribing point – Antibiotic therapy
PPIs should be withheld temporarily during courses of broad spectrum antibiotics in patients at increased risk of *C difficile*.

PPI Prescribing Points [1,8,10]
► Address lifestyle and review medications for possible causes of dyspepsia before prescribing a PPI.
► PPIs should be reviewed: after 4 weeks for newly initiated PPIs and at least once a year for repeat prescriptions.
► PPIs should be taken 30 to 60 minutes before breakfast or evening meal for maximum benefit.

Choice of PPI?
When given at standard doses, differences between the PPIs in terms of clinical efficacy and safety are minimal.[6] The NICE guidance on Dyspepsia and GORD provides information on relative dosage equivalence of PPIs – see **TABLE TWO**.

Northern Ireland Formulary choices
Lansoprazole and omeprazole are Northern Ireland Formulary choices. It is not recommended to initiate esomeprazole in primary care. However, if a patient is discharged from a Gastroenterology / Upper GI / Surgical Specialist with a written indication (e.g. recurring strictures) to be on esomeprazole for a specified reason and for a specified duration, this should not be changed in primary care.[28]

TABLE TWO: Dosage information on PPIs [1]

PPI	Full dose	Low dose
Esomeprazole	20mg once a day	Not available
Lansoprazole	30mg once a day	15mg once a day
Omeprazole	20mg once a day	10mg once a day
Pantoprazole	40mg once a day	20mg once a day
Rabeprazole	20mg once a day	10mg once a day

When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg; 40 mg is recommended as a double dose of esomeprazole.[1]

Reasons to remain on a long term full dose PPI (list not exhaustive)
- Gastroprotection due to co-medication[1] (see **TABLE ONE** for examples)
- Post dilatation of an oesophageal stricture[1]
- Barrett's oesophagus[8]
- History of ulcer complication (such as bleeding or perforation)[8]
- Zollinger-Ellison syndrome[8]
- Severe oesophagitis[10]
- Gastrointestinal manifestations of scleroderma.[1]

Functional Dyspepsia

Functional dyspepsia (also known as non-ulcer dyspepsia) is when no obvious cause of the symptoms is identified, i.e. endoscopy has ruled out cancer, PUD and oesophagitis. It is the most common finding arising from endoscopy for dyspepsia.[1,7]
Patients with heartburn as the predominate symptom and no findings on endoscopy should be managed as GORD.[1]

What causes functional dyspepsia?
The cause of functional dyspepsia is uncertain, and is most likely multifactorial. Gastrointestinal dysmotility and sensitivity to distension and acid have been suggested.[21] Abnormal central processing has also been suggested.[21]
There is a strong overlap between dyspepsia and irritable bowel syndrome (IBS).[21] However, patients whose pain is relieved by defaecation is more suggestive of IBS. [1]

The role of *H. pylori* in functional dyspepsia
There is an *association* between *H. pylori* and functional dyspepsia, however, the actual role it plays is not clear. *H. pylori* gastritis is detected in around 50% of people with functional dyspepsia. However, *H. pylori* is also common in otherwise asymptomatic people. Whether *H. pylori* infection causes symptoms in people without ulcer disease is controversial.[7]

Symptoms of functional dyspepsia
The Rome III diagnostic criteria further subdivides functional dyspepsia into postprandial distress syndrome (characterised by postprandial fullness and early satiation), and epigastric pain syndrome (characterised by epigastric pain or burning).[73,76,77]

How is functional dyspepsia managed?
Due to the likely multifactorial causes of functional dyspepsia, individual treatments are often only effective in a small proportion of patients.[21]
Patients with functional dyspepsia often require long term treatment (with regular review). However, available treatment options are usually based on extrapolation of data from short term studies.[1]

H. pylori eradication has been found to have a small benefit in reducing symptoms in functional dyspepsia.[7] A Cochrane review indicated a NNT of 14 for eradication therapy in functional dyspepsia, i.e. 14 people need to be treated with *H. pylori* eradication therapy to cure one extra case of functional dyspepsia.[7,24] Nevertheless, short course eradication therapy is seen as preferable to long term PPI therapy, therefore NICE recognise 'test and treat' as a cost-effective option in managing patients with functional dyspepsia.

NICE Guidance – Functional dyspepsia
- **Test and treat for *H. pylori*.**
  - If positive – one week eradication, followed by symptomatic management and periodic monitoring.
  - If negative – low dose PPI or H_2RA for 4 weeks.
- If symptoms continue or recur after initial treatment, offer a PPI or H_2RA to be taken at the lowest dose possible to control symptoms. 'As-needed' use of PPIs should also be discussed.[1]

Is there a need for retesting for *H. pylori*?

Routine re-testing is not required for patients with functional dyspepsia. However, the information it provides may be valued by individual people (e.g. those concerned with having 'an infection').[1]

What is the prognosis with functional dyspepsia?

In contrast to peptic ulcer disease, there is no cure for functional dyspepsia, and treatment is often needed on a long-term basis. The annual risk of recurrence for functional dyspepsia is 50%.[7]

The role of motility stimulants?

Due to new safety data, domperidone and metoclopramide are no longer recommended to be used as anti-motility agents for dyspepsia. Metoclopramide is associated with neurological effects such as short-term extrapyramidal disorders and tardive dyskinesia. In order to minimise these side effects, metoclopramide should only be prescribed for short-term use (up to 5 days) for nausea and vomiting.[19,20]

Domperidone is associated with a small risk of serious cardiac side effects. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced (maximum 30mg daily and maximum 7 days).[14,15,18]

Do antidepressants have any place in therapy for functional dyspepsia?

Studies are inconclusive and NICE do not include antidepressants in their guideline for Dyspepsia and GORD. However, a recent study suggested that tricyclic antidepressants (but not SSRIs) are beneficial in patients with functional dyspepsia.[21,25,26] Further studies are needed.

Gastro-Oesophageal Reflux Disease

What is GORD?

Gastro-oesophageal reflux disease (GORD) describes the reflux of gastric contents into the oesophagus, causing symptoms such as heartburn and acid regurgitation.[5] GORD refers to patients who have predominant reflux symptoms in whom endoscopy has shown either:

- Oesophageal inflammation (oesophagitis)
  OR
- No inflammation (endoscopy negative reflux disease).[1]

According to NICE, patients with uninvestigated 'reflux-like' symptoms should be managed as patients with uninvestigated dyspepsia.[1]

What causes GORD?

GORD is caused by a failure of the gastro-oesophageal junction to prevent acid reflux.[5,21]

How is GORD managed?

The evidence supports routine use of full-dose PPI therapy for 4 to 8 weeks to achieve healing in patients with endoscopically-detected GORD.[1] There is currently no evidence that H pylori causes or aggravates GORD. Therefore 'test and treat' is not recommended as a management option for patients with GORD.[1]

NICE Guidance – GORD

- People with GORD should be offered:
  - **A full-dose PPI for 4 or 8 weeks** (depending on severity of oesophagitis).
- If symptoms recur after successful treatment, patients should be advised to step down PPI therapy to the lowest dose to control symptoms. 'As-needed' use of PPIs should also be discussed.[1]
- If there is an inadequate response to a PPI, a H_2 receptor antagonist (H_2RA) may be offered instead.[1]

A protective role of *H. pylori* in GORD?

Studies have indicated that the prevalence of *H pylori* infection is significantly lower in patients with GORD compared to those without GORD. It has been suggested that *H. pylori* confers protection against GORD by way of decreased acid secretion as a result of corpus gastritis. Therefore, eradication of *H. pylori* in GORD could potentially lead to increased acid secretion and worsening of GORD symptoms.[17]

Adding a H_2RA at bedtime

PPIs are significantly more effective than H_2RA at healing oesophagitis and at improving symptoms of endoscopy-negative reflux disease.[5] However, despite PPI therapy being very effective at reducing acid output during the day, around 90% of patients with GORD have nocturnal acid breakthrough, even with twice daily PPI dosing. It can be managed in the short-term by the addition of a H_2RA at bedtime [in contrast to PPIs, H_2RAs do not need the presence of food in the stomach to work]. However, the effectiveness for this indication decreases after one to two weeks of treatment.[1,5]

Does GORD recur?

GORD is common and symptoms will recur within 1 year in up to 80% of people.[1,5] Also, between 10% and 40% of people with GORD fail to respond symptomatically (either partially or completely) to standard dose PPI treatment.[5]

Compliance with anti-secretory agent should first be evaluated. For people with persistent, severe symptoms, consider doubling the dose of the PPI or switching to an alternative PPI for a further month.[5]

A full-dose PPI may be required as long-term maintenance treatment for people with severe oesophagitis.[1]

Laparoscopic fundoplication

Nissen's fundoplication is an operation to treat severe GORD, where the surgeon wraps the top part of the stomach around the lower part of the oesophagus to tighten the sphincter. Laparoscopic fundoplication may be considered for people who:

- Respond to acid suppression therapy but do not wish to take long term drug therapy
- Have a confirmed diagnosis of acid reflux but who cannot tolerate acid suppression therapy.[1]

NB – laparoscopic fundoplication is unlikely to be suitable for people who do not respond to acid-suppression therapy (as this would indicate that the problem is not acid-related and therefore unlikely to respond to the procedure).

Surveillance for people with Barrett's oesophagus

For people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), surveillance to check progression to cancer will be determined by the diagnosing clinician in secondary care.

Peptic Ulcer Disease

Proven gastric or duodenal ulceration is defined as ulceration of the mucosa of the stomach or duodenum (respectively) confirmed by endoscopic examination, and known collectively as peptic ulcer disease (PUD).[6]

What causes PUD?

Most peptic ulcers are caused by the bacterium *Helicobacter pylori* (*H. pylori)*, with a few cases caused by NSAIDs.[21] *H. pylori* causes inflammation of the mucosal lining of the stomach, leading to depletion of the protective alkaline mucus layer and alteration of gastric acidity.[6]

How is PUD managed?

Management of PUD will depend on whether or not the patient is taking a NSAID. For people taking a NSAID who also test positive for *H. pylori*, eradication therapy reduces the additional risk posed by *H. pylori* above that posed by the NSAID, i.e. the NSAID is the greatest risk in these patients. Therefore, eradication therapy should commence **after** 8 weeks of a full dose PPI.[1]

Is there a need for re-testing for *H.pylori?*

Chronic *H.pylori* that causes an ulcer is a risk factor for gastric cancer.[5] Therefore, patients with gastric or duodenal ulcers should be re-tested *for H. pylori* 6 to 8 weeks after starting eradication therapy.[1]

Is there a need for repeat endoscopy?

Patients with *gastric* ulcers should have a repeat endoscopy 6 to 8 weeks after starting eradication therapy to ensure healing and further exclude the possibility of gastric cancer.[1] A repeat endoscopy is not required in patients with duodenal ulcers.[1]
If the ulcer remains unhealed, exclude non-adherence, malignancy, failure to detect *H. pylori*, inadvertent NSAID use, other ulcer-inducing medication and rare causes such as Zollinger–Ellison syndrome or Crohn's disease.[1]

NICE Guidance – Peptic Ulcer Disease

Patients not taking a NSAID:

- **Test for *H. pylori*:**
  - If positive – offer one week eradication therapy
  - If negative – offer full dose PPI for 4 to 8 weeks

Patients taking a NSAID:

- Stop the NSAID if possible.
- **Test for *H. pylori*:**
  - If positive – treat with full dose PPI for 8 weeks, **then offer one week eradication therapy**
  - If negative – treat with full dose PPI for 8 weeks.
- If symptoms recur after successful treatment, patients should be advised to step down PPI therapy to the lowest dose needed to control symptoms. 'As-needed' use of PPIs should also be discussed.[1]
- If there is an inadequate response to a PPI, a H_2 receptor antagonist (H_2RA) may be offered instead.[1]

Healing rates in peptic ulcer disease

Peptic ulcer disease is of importance because it leads to recurrent episodes of dyspepsia, and is associated with significant complications of bleeding and perforation.[1]
The discovery of *H. pylori* in 1983 revolutionised the treatment of peptic ulcer disease as it meant that ulcers could be healed and also prevented from recurring.[1]
A Cochrane review found a NNT for eradication therapy of 2 and 3 for duodenal and gastric ulcers respectively.[23]

H. pylori Testing and Eradication Therapy

H. pylori presence in the general population

H. pylori is widely present in the general population, often causing no harm, but is associated with peptic ulcer disease.[1] Some evidence suggests that *H pylori* infection is associated with social deprivation and that its prevalence increases with age.[1] It is estimated that 50% of people over the age of 60 in Western countries, and nearly 90% of all adults in developing countries are infected with *H. pylori*.[1]

Which test to use for *H. pylori*?

NICE recommend the use of either a carbon-13 urea breath test or a faecal antigen test for *H. pylori* in primary care.[1] The Health Protection Agency (HPA) Helicobacter Working Group does not recommend the routine use of serology testing because of the poor positive predictive value in populations with low prevalence. Serology testing has therefore been stopped in Northern Ireland. Serology indicates if an individual has ever encountered the antigen, rather than diagnosing active disease, therefore leading to false positive results.[1]
Locally in Northern Ireland a faecal antigen testing service is currently being commissioned [at time of this publication] and is expected in 2015.

Washout periods before testing following recent PPI and antibiotic use

Anti-secretory agents: a two week washout period should be left after **PPI** use and before testing for *H. pylori* with either a breath test or a stool antigen test.[1] This applies to all tests. Some companies had previously claimed that a two week washout period was not required before the urea breath test if the patient used a special test meal containing a greater concentration of acid. However, the evidence for this is lacking and there is a risk of false negative results if the PPI is not stopped. The MHRA considered that the

advertising was not consistent with the current product SPC and as such, advertising has been withdrawn.[79]

Antibiotics: a four week washout period should be left after antibiotic or bismuth use before testing for *H. pylori* with a breath test or a stool antigen test.

Resistance to *H.pylori*

Resistance to clarithromycin and metronidazole has increased substantially in recent years, with a subsequent fall in the *H. pylori* eradication rate.[22] Eradication rates with clarithromycin-containing triple regimens have fallen to less than 80% due to increased resistance. Resistance to amoxicillin is however still quite rare.[22,,27]

Antibiotic regimens

TABLE THREE shows the regimens and doses for *H. pylori* eradication as recommended by Public Health England.[81] A PPI plus amoxicillin and clarithromycin is the recommended first line regimen if suitable for the patient.[1,81]

TABLE THREE: Eradication regimens [81]

First and second line:	Penicillin allergy:	Penicillin allergy & previous metronidazole + clarithromycin:	Relapse & previous metronidazole + clarithromycin:
PPI full dose BD PLUS amoxicillin 1g BD PLUS either clarithromycin 500mg BD OR metronidazole 400mg BD	PPI full dose BD PLUS clarithromycin 250mg BD AND Metronidazole 400mg BD	PPI full dose BD PLUS bismuthate (De-nol tab®) 240mg BD PLUS metronidazole 400mg BD PLUS tetracycline hydrochloride 500mg QDS	PPI full dose BD PLUS amoxicillin 1g BD PLUS tetracycline hydrochloride 500mg QDS OR levofloxacin 250mg BD
For 7 days			
Do not use clarithromycin, metronidazole or quinolone if used in past year for any infection			

[Please note this table in the online COMPASS Therapeutic Notes differs from that in the published COMPASS Therapeutic Notes due to updated guidance from Public Health England on *H pylori* eradication since the publication of the COMPASS Therapeutic Notes]

References

1. NICE. NICE CG184 Dyspepsia and GORD, 2014. http://www.nice.org.uk/guidance/CG184
2. BSG. Dyspepsia management guidelines. Last updated 2002. http://www.bsg.org.uk/
3. BSO / HSCB. Prescribing data.
4. Clinical Knowledge Summaries. Dyspepsia - unidentified cause. http://cks.nice.org.uk/
5. Clinical Knowledge Summaries. Dyspepsia - proven GORD. http://cks.nice.org.uk/
6. Clinical Knowledge Summaries. Dyspepsia - proven peptic ulcer. http://cks.nice.org.uk/
7. Clinical Knowledge Summaries. Dyspepsia - proven non-ulcer. http://cks.nice.org.uk/
8. All Wales Therapeutics and Toxicology Centre. All Wales proton pump inhibitor and dyspepsia resource pack. Material to support appropriate prescribing of proton pump inhibitors across Wales. April 2013.
9. NICE. NICE CG27 Referral for suspected cancer. June 2005. http://www.nice.org.uk
10. Oh S. Proton pump inhibitors; uncommon side effects. Aust Fam Phy, 2011;40(9)705-708.
11. MHRA. Proton pump inhibitors in long-term use: reports of hypomagnesaemia. Drug Safety Update, April 2012. http://www.mhra.gov.uk
12. MHRA. Proton pump inhibitors in long-term use: recent epidemiological evidence of increased risk of fracture. Drug Safety Update, April 2012. http://www.mhra.gov.uk
13. Linsky A et al. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010;170:772-8.
14. MHRA. Press release: New advice for domperidone. Issued 25/4/2014. http://www.mhra.gov.uk
15. EMA. CMDh confirms recommendations on restricting use of domperidone-containing medicines. Issued 25/4/2014. http://www.ema.europa.eu
16. McColl KEL and Gillen D. Evidence that proton-pump inhibitor therapy induces the symptoms it is used to treat. Gastroenterology, 2009;137:20-39.
17. Richter JE. Effect of Helicobacter pylori eradication on the treatment of gastro-oesophageal reflux disease. Gut, 2004;53:310-311.
18. MHRA. Domperidone: risks of cardiac side effects—indication restricted to nausea and vomiting, new contraindications, and reduced dose and duration of use. Drug Safety Update, May 2014. http://www.mhra.gov.uk.
19. MHRA. Metoclopramide: risk of neurological adverse effects—restricted dose and duration of use. Drug Safety Update, August 2013. http://www.mhra.gov.uk.
20. EMA. European Medicines Agency recommends changes to the use of metoclopramide. Press release, 26/07/2013.
21. Ford AC and Moayyedi P. Dyspepsia. BMJ, 2013;347:f5059.
22. Gatta L et al. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. BMJ,2013;347:f4587.
23. Ford AC et al. Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. Am J Gastroenterol, 2004;99:1833-55.
24. Moayyedi P et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev 2006;2:CD002096.
25. Locke GR et al. The functional dyspepsia treatment trial (FDTT) key results. Gastroenterology, 2013;144(suppl 1):S140.
26. Soo S et al. Psychological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev, 2005;2:CD002301.
27. Graham DY and Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut 2010;59:1143e1153.
28. HSCB. Northern Ireland Formulary / Gastrointestinal chapter (updated 2014). http://niformulary.hscni.net
29. NICE. NICE Clinical Guideline CG27 Referral guidelines for suspected cancer, June 2005. http://www.nice.org.uk/Guidance/CG27

30. NPC. The management of dyspepsia in primary care. MeReC Briefing, no. 32, 2006. http://www.npc.co.uk/
31. Maconi G, Manes G and Porro GB. Role of symptoms in diagnosis and outcome of gastric cancer. World J Gastroenterol., 2008;14(8):1149–1155.
32. de Caestecker, J. ABC of the upper gastrointestinal tract. Oesophagus: heartburn. BMJ, 2001; 323(7315), 736-739.
33. Delaney BC et al. Helicobacter pylori test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). BMJ, 2008; 336(7645)
34. HPA. Test and treat for Helicobacter pylori (HP) in Dyspepsia. Quick Reference Guide for Primary Care. For consultation and local adaption. Health Protection Agency (2012). www.hpa.org.uk
35. Kushner PR and Peura DA. Review of proton pump inhibitors for the initial treatment of heartburn: is there a dose ceiling effect? Advances in Therapy, 2011; 28(5), 367-388.
36. Linsky A, Gupta K and Lawler EV. Proton pump inhibitors and risk for recurrent Clostridium difficile infection Archives of Internal Medicine, 2010;170(9), 772-778.
37. Malfertheiner P et al. Management of Helicobacter pylori infection - the Maastricht IV/Florence Consensus Report. Gut, 2012; 61(5), 646-664.
38. Manes G et al. Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment. British Medical Journal, 2003;326(7399), 1118.
39. Maton PN and Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. Drugs, 1999;57(6), 855-870.
40. McNulty C et al.Test and treat for dyspepsia - but which test? BMJ, 2005;30(7483), 105-106.
41. Moayyedi P. et al. Systematic review: antacids, H2-receptor antagonists, prokinetics, bismuth and sucralfate therapy for non-ulcer dyspepsia. Alimentary Pharmacology & Therapeutic, 2003;17(10), 1215-1227.
42. Talley NJ, Phung N and Kalantar JS. ABC of the upper gastrointestinal tract. Indigestion: when is it functional? BMJ, 2001;323(7324), 1294-1297.
43. Tran T, Lowry AM and El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. Alimentary Pharmacology & Therapeutics, 2007;25(2), 143-153.
44. Vergara M, Vallve M, Gisbert JP and Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Alimentary Pharmacology & Therapeutics, 2003;18(6), 647-654.
45. Yuan Y et al. Optimum duration of regimens for Helicobacter pylori eradication (Review). Cochrane Database Syst Rev, 2013; CD008337.pub2.
46. Stevens V and Van Wijngaarden E. Proton pump inhibitor use may be associated with an increased risk of Clostridium difficile infection. Evid Based Med, 2013;18(5)193-194.
47. Veldhuyzen van Zanten, SJ et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ, 2000; 162: S3-23.
48. Talley NJ et al. AGA technical review: evaluation of dyspepsia. American Gastroenterological Association. Gastroenterology, 1998; 114: 582-595.
49. Agreus, L. Socio-economic factors, health care consumption and rating of abdominal symptom severity. A report from the abdominal symptom study. Fam Pract,1993; 10: 152-163.
50. Drossman DA., et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig.Dis Sci., 1993; 38: 1569-1580.
51. Jones R. and Lydeard S. Dyspepsia in the community: a follow-up study. Br J Clin Pract, 1992; 46:95-97.
52. Chiba N. Definitions of dyspepsia: time for a reappraisal. Eur.J Surg.Suppl, 1998; 14-23.
53. Tytgat GN. GERD remains an intriguing enigma. Gastroenterology, 2001; 120:787.
54. Chiba N et al. A Canadian physician survey of dyspepsia management. Can.J Gastroenterol., 1998; 12: 83-90.
55. Moayyedi P et al. Effect of population screening and treatment for Helicobacter pylori on dyspepsia and quality of life in the community: a randomised controlled trial. Leeds HELP Study Group. Lancet, 2000; 355: 1665-1669.
56. Moayyedi P, et al. The proportion of upper gastrointestinal symptoms in the community associated with Helicobacter pylori, lifestyle factors, and nonsteroidal anti-inflammatory drugs. Leeds HELP Study Group. Am J Gastroenterol., 2000; 95: 1448-1455.
57. Rabeneck L, Wray NP and Graham D Y. Managing dyspepsia: what do we know and what do we need to know? Am J Gastroenterol., 1998; 93: 920-924.
58. Quine MA et al. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. Gut, 1995; 36: 462-467.
59. Goves J et al. First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: a multicentre study in general practice. Aliment.Pharmacol.Ther, 1998; 12: 147-157.
60. Meineche-Schmidt, V. and Krag, E. Antisecretory therapy in 1017 patients with ulcerlike or reflux like dyspepsia in general practice. Eur.J Gen.Pract, 1997; 3: 125-130.
61. Castell DO et al. Esomeprazole (40 mg) compared with lansoprazole (30mg) in the treatment of erosive esophagitis. Am J Gastroenterol., 2002; 97: 575-583.
62. Sharma VK, Leontiadis GI and Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. Aliment.Pharmacol.Ther, 2001;15: 227-231.
63. Edwards SJ, Lind T and Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. Aliment.Pharmacol.Ther, 2001;15: 1729-1736.
64. Bytzer, P. On-demand therapy for gastrooesophageal reflux disease. Eur.J Gastroenterol.Hepatol., 2001; 13 Suppl 1: S19-S22.
65. Bardhan KD et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. BMJ, 1999; 318: 502-507.
66. Bardhan K D. Intermittent and on-demand use of proton pump inhibitors in the management of symptomatic astroesophageal reflux disease. Am J Gastroenterol., 2003; 98: S40-S48.
67. Cremonini F et al. Helicobacter pylori-related diseases. Eur.J Clin Invest, 2001; 31: 431-437.
68. Lassen AT et al. Helicobacter pylori test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. Lancet, 2000; 356: 455-460.
69. McColl KE et al. Randomised trial of endoscopy with testing for Helicobacter pylori compared with non-invasive H pylori testing alone in the management of dyspepsia. BMJ, 2002; 324: 999-1002.
70. MeReC. Managing dyspepsia: the role of Helicobacter pylori. MeReC Bulletin 2001; 12: 1-4.
71. Chan FK and Leung WK. Peptic-ulcer disease. Lancet, 2002; 360: 933-941.
72. McColl KE. Motion--Helicobacter pylori causes or worsens GERD: arguments against the motion. Can.J Gastroenterol., 2002; 16: 615-617
73. Overland MK. Dyspepsia. Med Clin N Am, 2014;98;549-564.
74. Moshiree B, Barboza J and Talley N. An update on current pharmacotherapy options for dyspepsia. Expert Opin Pharmacother., 2013;14(13):1737-53.
75. Wee EW. Evidence-based approach to dyspepsia: from Helicobacter pylori to functional disease. Postgrad Med., 2013;125(4):169-80.
76. Tack J and Talley NJ. Functional dyspepsia--symptoms, definitions and validity of the Rome III criteria. Nat Rev Gastroenterol Hepatol. 2013 Mar;10(3):134-41.
77. Rome Foundation. Rome III disorders and criteria. Accessed 15/9/2014 http://www.theromefoundation.org/criteria/
78. BIA / HPA. Test and treat for Helicobacter pylori in dyspepsia. Quick reference guide for primary care. November 2014.
79. MHRA. Advertising investigations: Helicobacter Test INFAI (13C-urea), healthcare professional

advertisement, August 2014 http://www.mhra.gov.uk/Howweregulate/Medicines/Advertisingofmedicines/Advertisinginvestigations/CON467371

80. Savarino V et al. The 13C urea breath test in the diagnosis of Helicobacter pylori infection. Gut 1999;45:I18-I22 doi:10.1136/gut.45.2008.i18.

81. Public Health England. Management of infection guidance for primary care for consultation and local adaptation. Published October 2014. Management of infection guidance for primary care for consultation and local adaptation.

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COMPASS THERAPEUTIC NOTES ASSESSMENT
Management of Upper Gastrointestinal disorders

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
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1	**In the management of uninvestigated dyspepsia**			
	a	Use of pillows may be helpful in alleviating symptoms of reflux at night	T	F
	b	NICE recommend either empirical full dose PPI therapy for 4 weeks or 'test for and treat' for *H.pylori* in patients presenting with dyspepsia for the first time (in the absence of red flags)	T	F
	c	All patients aged < 55 years should be referred for endoscopic investigation of dyspepsia	T	F
	d	Of those undergoing endoscopy, 60% have no identified cause of their symptoms	T	F
2	**With regards to proton pump inhibitor (PPI) therapy**			
	a	PPIs can be used 'as-needed' when appropriate	T	F
	b	The risk of hypomagnesaemia with PPIs is increased when co-prescribed with digoxin or diuretics	T	F
	c	The risk of acquiring *C. difficile* associated diarrhoea is two to three times higher in PPI users compared to non-users	T	F
	d	PPIs should be taken 30 to 60 minutes before food for maximum benefit	T	F
3	**In the management of functional dyspepsia**			
	a	There is a strong overlap between dyspepsia and irritable bowel syndrome	T	F
	b	Due to the likely multifactorial causes of functional dyspepsia, individual treatments are often only effective in a small proportion of patients	T	F
	c	*H. pylori* eradication has been found to have a small benefit in reducing symptoms in functional dyspepsia	T	F
	d	Domperidone or metoclopramide may be used in patients with functional dyspepsia	T	F
4	**In the management of gastro-oesophageal reflux disease (GORD)**			
	a	*H.pylori* is the main cause of GORD	T	F
	b	The addition of a H_2RA at bedtime can be beneficial for patients with nocturnal acid breakthrough	T	F
	c	GORD is common and symptoms will recur within 1 year in up to 80% of people	T	F
	d	Laparoscopic fundoplication may be considered in people with GORD who do not respond to PPI therapy	T	F
5	**In the management of peptic ulcer disease (PUD)**			
	a	Management strategies for PUD depend on whether or not the person is taking a NSAID	T	F
	b	Patients with gastric or duodenal ulcers should be re-tested for *H. pylori* 6 to 8 weeks after starting eradication therapy	T	F
	c	A four week washout period should be left after PPI use and before testing for *H. pylori* with either a breath test or a stool antigen test	T	F
	d	Recent use of clarithromycin should be checked before prescribing in triple therapy regimen for *H.pylori* eradication.	T	F