Gloucestershire Hospitals
NHS Foundation Trust

Clinical guideline: The prescription of oral proton pump inhibitors (PPIs)

Introduction

The high efficacy and low toxicity of proton pump inhibitors (PPIs) has contributed to their frequent prescription worldwide, often without clear indication. Such widespread over-prescription incurs avoidable financial and clinical costs[1,2]. PPI use is associated with a number of adverse consequences including *Clostridium difficile* infection, community acquired pneumonia, osteoporosis, hypomagnesaemia and kidney injury[3-8]. **In light of this, PPI prescription should be reserved for patients where there is a clear indication and clinicians should consider stopping PPIs when the indication is unclear. There are data to support stopping PPIs in patients who have been taking them long term**[9-11]

Preliminary points:

1. Use oral PPIs as first line

2. If the oral route is compromised (e.g. by vomiting, low GCS) then consider using:
   First line: lansoprazole orodispersible tablet orally or via nasogastric tube, or oral PPI with anti-emetic
   Second line: IV PPI bolus

3. Rebound hypersecretion (a rise in acid secretion after discontinuing PPI treatment) can occur after courses as short as eight weeks' duration. This can often lead to an increase in GI symptoms, which may be mistaken for disease relapse. Patients should be warned about the possibility of rebound hypersecretion when PPIs are deprescribed. The duration of rebound hypersecretion is unknown, but some studies show reflux-like symptoms within two weeks, and for at least four weeks after withdrawal from PPI therapy. To help limit the occurrence of rebound hypersecretion, the dose of PPI should be tapered to a lower dose and an antacid and/or alginate (e.g. Peptac®) could also be prescribed for at least two weeks. If a step-down approach does not adequately control symptoms, PPI treatment could be resumed on an 'on demand' basis, or with the lowest effective dose with consideration to future step-down when appropriate. Patients should be advised to purchase OTC any supplies of antacid/alginate required to help manage their occasional symptoms on an ongoing basis.

4. The PPI dosing categories are referenced in guideline (**table 1**)[12]:

Table 1 - PPI doses

PPI	Full dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg once a day	Not available	40 mg once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg twice a day
Omeprazole	20 mg once a day	10 mg once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg twice a day

Indications for prescribing PPIs in Secondary Care:

1. Patients admitted with suspected upper GI bleeding

- Discontinue contributory medications where possible on a risk versus benefit basis
- PPIs should not be used prior to endoscopic diagnosis in patients presenting with acute upper gastrointestinal bleeding[13]

2. Peptic ulcer (gastric or duodenal) [12]

If taking Non-steroidal anti-inflammatory drugs (NSAIDs):

- Stop NSAIDs where possible
- Offer a double-dose PPI (or histamine-2 receptor anatagonist (H2RA)) therapy for 8 weeks
- Offer *H.pylori* eradication therapy to people who have tested positive for *H.pylori* and who have peptic ulcer disease.

If not taking NSAIDs

- Offer a double-dose PPI or H2RA for 4 to 8 weeks
- Offer *H.pylori* eradication therapy to people who have tested positive for *H.pylori* and who have peptic ulcer disease.

3. Mild gastro-oesophageal reflux disease (GORD) [12]

- Offer a full-dose PPI for 4 to 8 weeks
- If symptoms recur after initial treatment offer a PPI at the lowest dose necessary to control symptoms and consider an 'as required' dosing approach
- Offer H2RA therapy if there is an inadequate response to PPIs

4. Moderate-severe GORD (LA grade C and D) [13]

- Use esomeprazole 40mg once daily for 4 to 8 weeks, then continue long-term 20mg once daily

5. Barrett's oesophagus [14]

- Use of full-dose PPI is recommended for symptom control
- In asymptomatic patients with Barrett's oesophagus there is insufficient evidence to recommend routine PPI use

6. Dyspepsia[12]

- Discontinue contributory medications where possible
- Offer empirical full-dose PPI for 4 weeks
- If symptoms recur after the initial PPI course then recommence the PPI at the lowest dose necessary to control symptoms and consider 'as required' dosing
- Offer H2RA therapy if there is an inadequate response to a PPI

7. Functional dyspepsia[12]

- Offer *H. pylori* 'test and treat'
- If *H.pylori* has been excluded and symptoms persist offer either a low-dose PPI or H2RA for 4 weeks
- If symptoms persist offer a PPI or H2RA at the lowest dose necessary to control symptoms and consider 'as required' dosing
- Avoid long-term, frequent dose, continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them)

8. Oesophageal dilatation[12]

- Patients should continue on long-term full-dose PPI therapy

9. Use of PPIs for gastro-protection

Patients must be informed of the course length of the PPI so that treatment is not continued inadvertently long term unless necessary

NSAIDs[15-]

Risk factors for GI adverse effects:

- History of gastrointestinal bleeding, peptic ulcer or gastroduodenal perforation
- Aged 65 years or older
- Using maximum recommended NSAID dose

- Concomitant use of drugs known to increase the risk of gastrointestinal bleeding /dyspepsia (e.g. anticoagulants, aspirin, clopidogrel, prasugrel, ticagrelor corticosteroids, antidepressants (selective serotonin reuptake inhibitors, venlafaxine or duloxetine))
- Significant co-morbidity (e.g. diabetes, renal/hepatic impairment, cardiovascular disease, advanced cancer or hypertension)
- Excessive alcohol consumption
- Heavy smoking
- Anticipated prolonged NSAIDs use, including patients with:
  - Rheumatoid arthritis or osteoarthritis
  - Low back pain, ankylosing spondylitis, psoriatic arthritis and other spondyloathropathies

- If the patient has a history of GI ulceration and more than two risk factors they are considered high-risk – prescribe a selective COX-2 NSAID and a PPI
- If the patient has 1-2 risk factors – prescribe a selective COX-2 NSAID alone or a standard NSAID with a PPI
- If the patient has no risk factors – prescribe an NSAID alone

Table 2 – Licensed PPI doses for gastro-protection

PPI	Dose for gastro-protection
Esomeprazole	20 mg once a day
Lansoprazole	15-30 mg once a day
Omeprazole	20 mg once a day
Pantoprazole	20 mg once a day
Rabeprazole	20 mg once a day

Corticosteroids[16-17]

- There is no high quality evidence to suggest that corticosteroids cause GI ulceration, although they do cause dyspepsia and may be associated with an increased risk of gastrointestinal bleeding or perforation in hospitalised patients
- Consider co-prescribing a PPI for patients on more than 3 weeks treatment or for those needing frequent courses (three or four per year) in those with risk factors for GI bleeding which include:
  - History of gastrointestinal bleeding, peptic ulcer or gastroduodenal perforation
  - Aged 65 years or over
  - Concomitant use of drugs known to increase the risk of gastrointestinal bleeding/dyspepsia (e.g. anticoagulants, aspirin, clopidogrel, prasugrel, ticagrelor, NSAIDs, antidepressants (selective serotonin reuptake inhibitors, venlafaxine or duloxetine))

- Significant co-morbidity (e.g. advanced cancer)
- Excessive alcohol consumption
- Heavy smoking

Dual anti-platelet therapy[18-19]

- Consider gastro-protection with PPI's in patients at higher than average risk of gastrointestinal bleeds:
  - History of gastrointestinal bleeding
  - Concomitant use of drugs known to increase the risk of gastrointestinal bleeding/dyspepsia (e.g. NSAIDs, antidepressants (selective serotonin reuptake inhibitors, venlafaxine or duloxetine))

  Or two of:
  - Aged 65 years or over
  - Dyspepsia
  - Gastro-oesophageal reflux disease
  - *Helicobacter pylori* infection
  - Chronic alcohol use
- Note: Concomitant use of clopidogrel with omeprazole or esomeprazole is not recommended[20]

10. Oesophagitis[12]

Mild/Moderate:

- Offer a full dose PPI for 4 to 8 weeks, then:
  - If clinical improvement has occurred then reduce the PPI dose to the lowest necessary to control symptoms and consider an 'as required' dosing approach
  - If there has been no clinical improvement then escalate PPI therapy to a double dose regimen or consider switching to an alternative PPI or H2RA

Severe:

- Please note specific PPI dosing for severe oesophagitis from **table 3** (below)
- Offer full dose PPI for 8 weeks for healing and then:
  - If healing has been achieved then continue the full dose as long-term maintenance therapy taking into account patient preferences and tolerability
  - If healing is not achieved then consider escalating therapy to a double dose of the initial PPI or switching to an alternative PPI at full or double dose

Table 3: PPI dosing for severe oesophagitis

PPI	Full dose	Low dose (on-demand dose)	Double dose
Esomeprazole	40 mg once a day	20 mg once a day	40 mg twice a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg twice a day
Omeprazole	40 mg once a day	20 mg once a day	40 mg twice a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg twice a day

11. PPI prescribing - caveats

Hypomagnesaemia[7, 21]

- Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs although the exact incidence is unknown
- In some cases hypomagnesaemia occurred after 3 months of PPI therapy, but most occurred after 1 year of treatment
- In most case reports, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI
- Consider optimising magnesium levels before starting treatment and periodically during prolonged treatment, especially in those taking digoxin or other drugs that can cause hypomagnesaemia (e.g. diuretics)
- PPIs must only be commenced and continued with a clear indication and their ongoing use regularly reviewed

Hyponatraemia[22]

- Hyponatraemia is considered to be a rare adverse effect of PPI's but due to considerable numbers of patients on treatment, it is likely that this effect will be seen in clinical practice
- It is not clear if there are differing risks of hyponatraemia with differing PPI's
- Cases in the literature are largely limited by case reports and small studies. Some studies suggest that elderly people are more at risk but this may be confounded by the fact that they are more likely to be taking a range of medicines that can cause hyponatraemia
- Current evidence does not support holding PPI's due to hyponatraemia where other medicines or the patient's clinical condition are more likely to be the cause of hyponatraemia.
- However, PPI's should be reviewed in patients with hyponatraemia of no apparent alternative cause, especially if the PPI is newly prescribed
- Again, it is important to only initiate and continue PPI's in patients with a clear indication

Community acquired pneumonia[6.23-24]

- Some observational studies and meta-analyses suggest that PPIs may be associated with an increased risk of community-acquired pneumonia, particularly within the first 30 days of PPI use, however these studies are confounded by bias and reflux disease and so no firm conclusions can be drawn. There is some data to suggest elderly people on long-term PPI therapy are also at higher risk of CAP but more research is needed.
- PPIs must only be commenced and continued with a clear indication and their ongoing use regularly reviewed

Clostridium difficile infection (CDI) [3, 10, 25-26]

- Public Health England guidelines recommend considering stopping PPIs and H2RA in patients with or at high risk of CDI
- The current evidence has confirmed an association between PPI use and CDI, especially in cases of re-infection, where the risk seems to be independent of length of PPI exposure
- In view of this, patients should only be commenced on a PPI and these continued long-term when there is a clear indication for their use.

Fracture risk[2, 4, 27-28]

- Observational studies suggest there may be a modest increase in the risk of hip, wrist or spinal fracture with PPIs especially if used in high doses and for prolonged durations. The increased risk was observed mainly in elderly patients but confounding factors may have contributed
- If the patient is considered at risk of osteoporosis ensure adequate intake of calcium and vitamin D is maintained and if necessary give additional bone-sparing medication

Kidney injury

Acute[8, 29-30]

- PPI use has been associated with acute interstitial nephritis (AIN)
- On the basis of current evidence, it is recommended to withhold PPI's in all cases of AKI stage 3 until the cause of AKI is established. If the cause of AKI is known (e.g. sepsis, dehydration, or other medicines), it is not necessary to withhold the PPI.

Chronic[5, 11 29-31]

- Although studies indicate that long-term PPI use is associated with a higher risk of CKD findings may be confounded by other factors such as NSAID use and hence there is a need for further investigation
- PPIs must be commenced and continued only with a clear indication and their ongoing use regularly reviewed

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