BMJ Best Practice

Peptic ulcer disease

Straight to the point of care

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Summary

Peptic ulcer disease usually presents as chronic, upper abdominal pain related to eating a meal (dyspepsia).

Use of non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection are the most common causes.

There may be some epigastric tenderness, but often there are no other signs on physical examination.

Endoscopy is diagnostic and may show an ulcer in the stomach or proximal duodenum. *H pylori* infection should be sought.

The most common complication is gastroduodenal bleeding. Perforation is a less frequent but potentially life-threatening complication. Either of these may be the presenting symptom, particularly in patients taking NSAIDs.

Definition

A break in the mucosal lining of the stomach or duodenum more than 5 mm in diameter, with depth to the submucosa. Ulcers smaller than this or without obvious depth are called erosions. Peptic ulcers result from an imbalance between factors promoting mucosal damage (gastric acid, pepsin, *Helicobacter pylori* infection, non-steroidal anti-inflammatory drug use) and those mechanisms promoting gastroduodenal defence (prostaglandins, mucus, bicarbonate, mucosal blood flow).

THEORY

Epidemiology

Accurate estimates require endoscopic studies because symptoms are insensitive and non-specific indicators of peptic ulcer. One systematic review of the literature reported an annual incidence of 0.10% to 0.19% for physician-diagnosed peptic ulcer disease and a 1-year prevalence of 0.12% to 1.50%.[1] The prevalence of gastric ulcer varies significantly worldwide; 4.1 % in Sweden and 6.1% in China.[2] [3]

The incidence of peptic ulcer increases with age; gastric ulcers peak in the fifth to seventh decades and duodenal ulcers 10 to 20 years earlier.[4] Both sexes are similarly affected.

The epidemiology of peptic ulcer disease largely reflects the epidemiology of the two major aetiologic factors, *Helicobacter pylori* infection and use of non-steroidal anti-inflammatory drugs (NSAIDs). In the developed world, *H pylori* incidence has been slowly declining over the past 50 years and NSAID use has increased. Most studies report that peptic ulcers are decreasing in prevalence over time.[4] [5] [6] [7] [8] [9]

Nevertheless they remain a problem, especially in the developing world where *H pylori* infection is highly prevalent.[10] A 2019 literature review of the epidemiology of peptic ulcer disease (PUD) in Africa found heterogeneity in the prevalence and incidence of PUD across the continent. However, most of the tertiary-centre studies found a higher prevalence of PUD in Africa when compared with similar studies in western countries.[11]

Risk factors

Strong

Helicobacter pylori infection

H pylori is known to have a role in the aetiology of peptic ulcer disease. If those taking non-steroidal anti-inflammatory drugs (NSAIDs) are excluded, about 90% of patients with duodenal ulcers and more than 70% with gastric ulcers have *H pylori* infection.[17] [19] Infection increases the lifetime risk of peptic ulcers.[10]

The likely mechanisms are through gastrin and acid hyper-secretion (duodenal ulcers) and local mucosal damage (gastric ulcers).

Eradication of infection prevents recurrence of both peptic ulcer disease and bleeding.

non-steroidal anti-inflammatory drug (NSAID) use

The incidence of ulcers in chronic NSAID users is about 20% compared with about 5% in non-users.[20] Low-dose aspirin use is also likely to increase the risk, particularly in older patients.[21]

The risk of NSAID-induced ulcers increases with increasing age (>60 years), a history of peptic ulcer, high doses of NSAIDs and longer duration of use, *Helicobacter pylori* infection, and concurrent use of corticosteroids, other anti-thrombotic drugs, and bisphosphonates.[21] [22] [23] [24] [25]

NSAIDs more commonly cause gastric ulcers than duodenal ulcers and do so by impairing mucosal defences, mainly mediated through cyclo-oxygenase (COX)-1. Selective cyclo-oxygenase-2 (COX-2) inhibitors are less likely to cause peptic ulcers.[26]

In patients using NSAIDs, peptic ulcer disease is more common in *H pylori* -positive than in *H pylori* -negative patients.[27]

Stopping NSAID use (and treating *H pylori* , if present) reduces ulcer recurrence. If NSAID use cannot be stopped, coprescription with a proton-pump inhibitor reduces recurrence.

smoking

Smoking is a risk factor for peptic ulcers. One population-based study found that the prevalence of ulcer disease in current and former smokers (11.4% and 11.5%) is nearly double that of people who have never smoked (6.0%).[28] The mechanisms are likely multifactorial.[29]

increasing age

The incidence of peptic ulcers and associated complications increase with age.

personal history of peptic ulcer disease

Mainly through persistent unrecognised *Helicobacter pylori* infection.

family history of peptic ulcer disease

Family history of peptic ulcer is a risk factor for peptic ulcer disease.[30] [31] Risk may be present in families with low *Helicobacter pylori* prevalence.[32]

patient in intensive care

Prophylactic use of a proton-pump inhibitor is appropriate for patients in intensive care, especially those who require mechanical ventilation, those who are deemed at high risk of gastrointestinal bleeding due to comorbidities such as chronic liver disease, or those who have co-existing conditions such as coagulopathy, sepsis, or acute kidney injury.[33] [34] The risk lessens as patient status improves.

Weak

rotating shift work

Evidence suggests that people who work rotating shift patterns, including night shifts, have a higher risk of peptic ulcer disease than people who work fixed day shifts.[35]

Aetiology

The two major aetiologic factors responsible for peptic ulceration are infection by the gram-negative gastric pathogen *Helicobacter pylori* and the use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). There is some synergy between these two major causes.[12]

Rarer causes include gastric ischaemia (responsible for the 'stress ulcers' that can occur in patients with multiple organ failure in intensive care units), Zollinger-Ellison syndrome (a syndrome of gastric acid hypersecretion caused by a gastrin secreting neuro-endocrine tumour), certain medications (e.g., potassium chloride, bisphosphonates), infections (cytomegalovirus in patients with HIV, and occasionally herpes simplex virus), and Crohn's disease. A small but increasing proportion of peptic ulcers seem truly idiopathic.[13] [14]

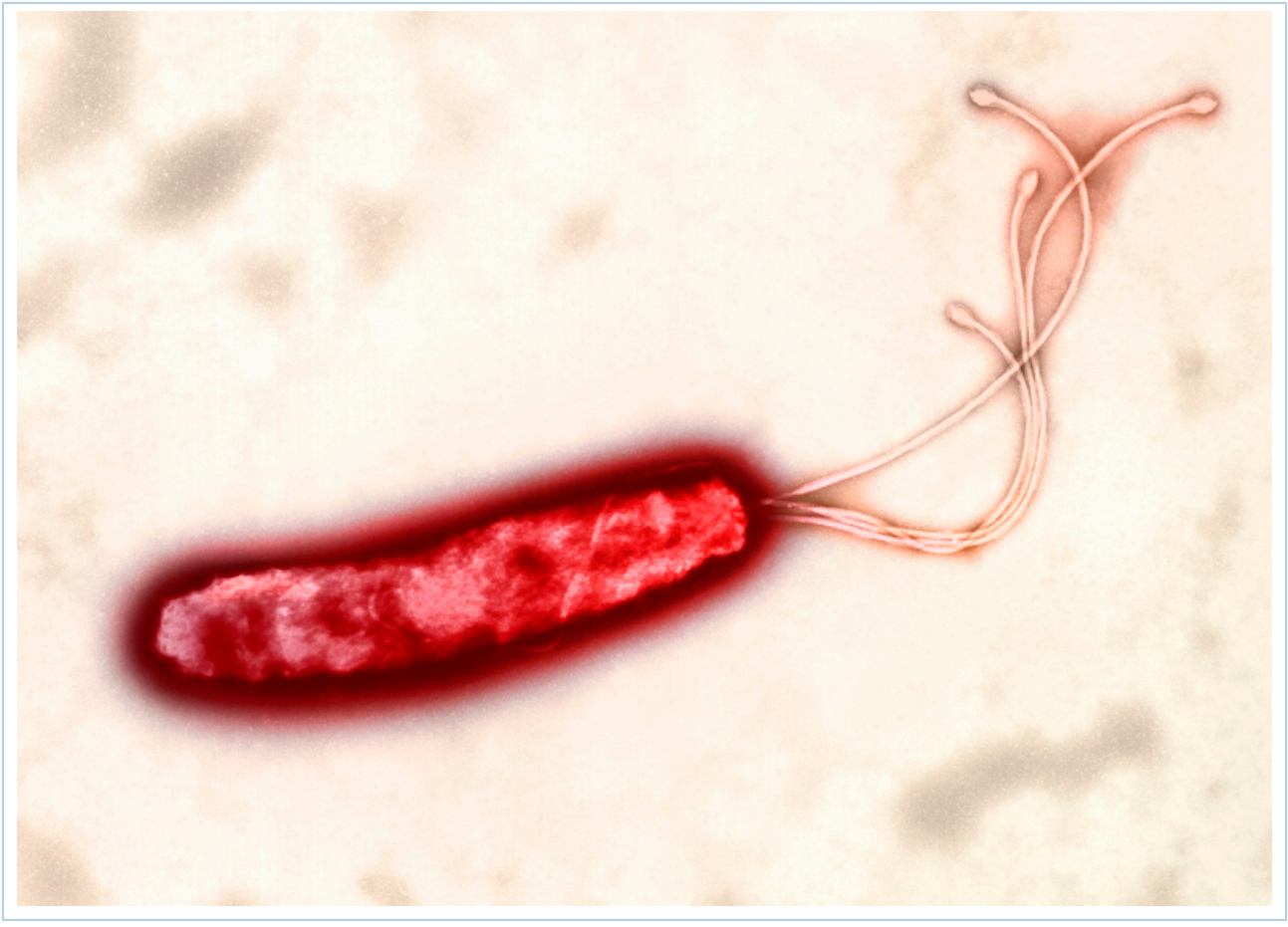
Psychological stress may play a role in some patients. A population-based prospective study in Denmark that included 3379 individuals demonstrated that psychological stress increased the incidence of peptic ulcer in

part by influencing health risk behaviours.[15] A higher incidence of ulcer disease is also reported after acute traumatic events such as bombing raids during World War 2 and following the Japanese tsunami.[16]

Pathophysiology

Peptic ulcers result from an imbalance between factors that can damage the gastroduodenal mucosal lining and defence mechanisms that normally limit the injury. Aggressive factors include gastric juice (including hydrochloric acid, pepsin, and bile salts refluxed from the duodenum), *Helicobacter pylori* , and non-steroidal anti-inflammatory drugs (NSAIDs).[17] Mucosal defences comprise a mucus bicarbonate layer secreted by surface mucus cells forming a viscous gel over the gastric mucosa. Also key is the integrity of tight junctions between adjacent epithelial cells, and the process of restitution, whereby any break in the epithelial lining is rapidly filled by adjacent epithelial and mucosal stromal cells that migrate to fill the gap. Mucosal defences rely heavily on an adequate blood supply.

In general, duodenal ulcers are the result of hypersecretion of gastric acid related to *H pylori* infection (the majority of patients), whereas secretion is normal or low in patients with gastric ulcers.[17]



Helicobacter pylori bacterium, transmission electron micrograph (TEM)

Heather Davies/Science Photo Library

In duodenal ulcers, chronic *H pylori* infection confined mainly to the gastric antrum leads to impaired secretion of somatostatin and consequently increased gastrin release, resulting in gastric acid hypersecretion. In Zollinger-Ellison syndrome, a gastrin-secreting neuro-endocrine tumour is the stimulus for high rates of gastric acid secretion.

In gastric ulcers, longstanding *H pylori* infection throughout the stomach accompanied by severe inflammation results in gastric mucin degradation, disruption of tight junctions between gastric epithelial cells, and the induction of gastric epithelial cell death. NSAIDs cause injury directly (involving trapping hydrogen ions) and indirectly (a systemic effect involving the inhibition of cyclo-oxygenases, especially COX-1) and increase bleeding risk through antiplatelet actions.[12] [18]

Classification

General

Peptic ulcers are generally categorised as gastric or duodenal.

Case history

Case history #1

A 40-year-old man presents to his primary care physician with a 2-month history of intermittent upper abdominal pain. He describes the pain as a dull, gnawing ache. The pain sometimes wakes him at night, is relieved by food and drinking milk, and is helped partially by famotidine. He had a similar but milder episode about 5 years ago, which was treated with omeprazole. Physical examination reveals a fit, apparently healthy man in no distress. The only abnormal finding is mild epigastric tenderness on palpation of the abdomen.

Other presentations

Duodenal ulcers may penetrate posteriorly into the pancreas, causing severe abdominal pain radiating through to the back. Gastric and duodenal ulcers may cause occult blood loss and iron deficiency anaemia. Rarely, patients may develop pyloric stenosis from an ulcer of the pyloric channel and present with nausea, vomiting, early satiety, and a succussion splash on physical examination (caused by gastric outlet obstruction). The combination of peptic ulcer symptoms with diarrhoea may indicate Zollinger-Ellison syndrome.

Importantly, peptic ulcers may cause no symptoms (especially in older people and those taking non-steroidal anti-inflammatory drugs). Then presentation may be sudden, with the signs of bleeding (haematemesis and/or melaena and shock) or perforation with peritonitis.

Recommendations

Key Recommendations

Recognise a **sudden presentation** of peptic ulcer disease to be potentially life-threatening and resuscitate according to ABC principles. Signs include:

- Bleeding (haematemesis and/or melaena)
- Shock
- Peritonitis (if perforation has occurred).

Refer any patient who presents in the community with dyspepsia together with significant acute gastrointestinal bleeding immediately (on the same day) to a specialist.[46]

Consider peptic ulcer disease in a patient with the following symptoms and signs:

- **Dyspepsia**, commonly related to eating and experienced at night. For more information about diagnosing dyspepsia, see Assessment of dyspepsia .
- Chronic or recurrent central, upper abdominal pain or discomfort, demonstrated by the patient with the 'pointing sign'.
- Nausea, anorexia, and vomiting are uncommon, but if present, nausea may be relieved by eating.

The following risk factors increase the likelihood of peptic ulcer disease:

- ***Helicobacter pylori* infection** - present in >90% of patients with duodenal ulcer and >70% with gastric ulcer[17] [19]
- **NSAID use**
- Smoking
- Increasing age
- Personal or family history of peptic ulcer disease
- An intensive care stay.

Be aware that:

- Weight loss, a low haemoglobin level, or a raised platelet count associated with any one of dyspepsia, reflux, or upper abdominal pain in a patient ≥55 years may suggest **malignancy** and should be investigated with an endoscopy within 2 weeks[47]
- Diarrhoea associated with dyspepsia may indicate Zollinger-Ellison syndrome
- Penetrating duodenal ulcers may cause severe pain radiating through to the back.

Endoscopy is the definitive diagnostic test for confirming peptic ulcer disease and identifying *H pylori* , with biopsy samples collected for rapid urease testing or histology.

- Note that in practice, the rapid urease test can be falsely negative if:
  - There is acute upper gastrointestinal bleeding
  - The patient is being treated with a PPI
  - The patient has received antibiotics that might reduce the density of *H pylori* colonisation.

Request the **urea breath test** or **stool antigen test** if the patient's *H pylori* status is uncertain or to re-test a patient to confirm that eradication therapy has been successful. If these are unavailable, laboratory-based serology can be used (provided its performance has been locally validated).[46]

- Do not perform the urea breath test or stool antigen test within 2 weeks of PPI or 4 weeks of antibiotics, as these drugs suppress bacteria and can lead to false negatives.[46] [48]

Full Recommendations

History

Non-steroidal anti-inflammatory drug (NSAID) use, *H pylori* infection, smoking, increasing age, personal or family history of peptic ulcer disease, and an intensive care stay are key risk factors.

A common clinical feature is dyspepsia, a chronic or recurrent abdominal pain, or discomfort centred in the upper abdomen.[49] It should be noted that most people with dyspepsia do not have peptic ulcer disease.[49]

Dyspepsia is commonly related to eating and is often nocturnal. However, the absence of epigastric pain does not rule out the diagnosis. Nausea and vomiting are uncommon; the former may be relieved by eating. Vomiting, if present, generally occurs after eating. Weight loss and anorexia may also be present.

The relief of symptoms after the use of antacids may support the diagnosis. However, this is neither a sensitive nor specific indicator.

Presentation may be sudden, with life-threatening bleeding.

Weight loss, a low haemoglobin level, or a raised platelet count associated with the above symptoms in a patient aged ≥55 years may suggest malignancy and should be investigated accordingly.[47] In particular, the UK National Institute for Health and Care Excellence (NICE) recommends **urgent upper gastrointestinal endoscopy (within 2 weeks) for any person aged ≥55 years who has weight loss together with any one of dyspepsia, reflux, or upper abdominal pain**.[47]

If diarrhoea is also present, this may indicate Zollinger-Ellison syndrome.

In patients with duodenal ulcers, the abdominal pain may be severe and radiate through to the back as a result of penetration of the ulcer posteriorly into the pancreas.

Rarely, nausea, vomiting, and early satiety indicate pyloric stenosis (a complication of peptic ulcer disease).

Importantly, peptic ulcers may cause **no symptoms**, especially in older people and those taking NSAIDs.

Physical examination

Presentation may be sudden, with:

- Bleeding (haematemesis and/or melaena)
- Shock
- Peritonitis (if perforation has occurred).

In more typical presentations, there may be some **epigastric tenderness** on palpation of the abdomen, but often there are no other signs on examination. The patient can generally show the site of pain with one finger ('pointing sign').

Atypical presentations of peptic ulcer disease also occur.

- Gastric and duodenal ulcers may cause occult blood loss and iron deficiency anaemia.
- Rarely, a succussion splash may be heard in patients with pyloric stenosis (caused by gastric outlet obstruction).

Investigations

Endoscopy

Refer any patient who presents with dyspepsia together with significant acute gastrointestinal bleeding immediately (on the same day) to a specialist.[46]

Refer for endoscopy **within 2 weeks** any patient aged ≥55 years who has weight loss together with any one of dyspepsia, upper abdominal pain, or reflux, to investigate possible malignancy.[47]

Endoscopy is the definitive diagnostic test for peptic ulcer disease and upper gastrointestinal tract neoplasms. Endoscopy:

- Is widely available
- Is more sensitive and specific for peptic ulcer disease than barium radiography
- Enables biopsy (for diagnosing malignancy and for *H pylori* detection).

A biopsy is taken during the index endoscopy.

- A rapid urease test or histology is used to identify *H pylori* infection.
- Note that in practice, the rapid urease test can be falsely negative if:
    - There is acute upper gastrointestinal bleeding.
    - The patient is being treated with a PPI.
    - The patient has received antibiotics that might reduce the density of *H pylori* colonisation.

Offer any patient who has gastric ulcer and *H pylori* a **repeat endoscopy 6 to 8 weeks** after beginning treatment, depending on the size of the lesion.[46]

Consider endoscopy subsequent to treatment if the patient continues to experience symptoms.

Barium radiography should be reserved for patients who are unable or unwilling to undergo endoscopy, and it is not routinely recommended.

Anti-thrombotic treatment with either warfarin or a direct oral anticoagulant (DOAC) or dual antiplatelet therapy is not a contraindication to endoscopy. Upper gastrointestinal endoscopy with or without diagnostic biopsies is regarded as a low-risk procedure for bleeding, and no or minimal alterations in the anti-thrombotic regimen are required for non-emergency diagnostic endoscopy.

- For low-risk endoscopic procedures such as diagnostic endoscopy with or without biopsy, the 2021 update to the British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommends:[50]
    - Continuing P2Y $_{12}$ receptor antagonists as single or dual antiplatelet therapy (DAPT)
    - Continuing warfarin therapy

- Check international normalised ratio (INR) 1 week before endoscopy
- If the INR result is within the therapeutic range then continue with the usual daily dose
- If INR is above the therapeutic range but <5 then reduce the daily dose until INR returns to therapeutic range
- If the INR is greater than 5 then defer the endoscopy and contact the anticoagulation clinic, or an appropriate specialist, for advice.

- Omitting the morning dose of DOACs.

Biopsy and histology

Obtaining samples for urease testing (rapid urease test) and histology is invasive, and is reserved for patients in whom endoscopy is otherwise indicated. Both urease testing and histology can detect *H pylori* ; however, histology can determine if the ulcer is neoplastic (very rarely) or if there is evidence that an NSAID is the likely cause.

Note that in practice, the rapid urease test can be **falsely negative** if there is acute upper gastrointestinal bleeding, if the patient is being treated with a PPI, or if the patient has received antibiotics that might reduce the density of *H pylori* colonisation.

Urea breath test or stool antigen test for H pylori

Establish whether the patient is infected with *H pylori* .

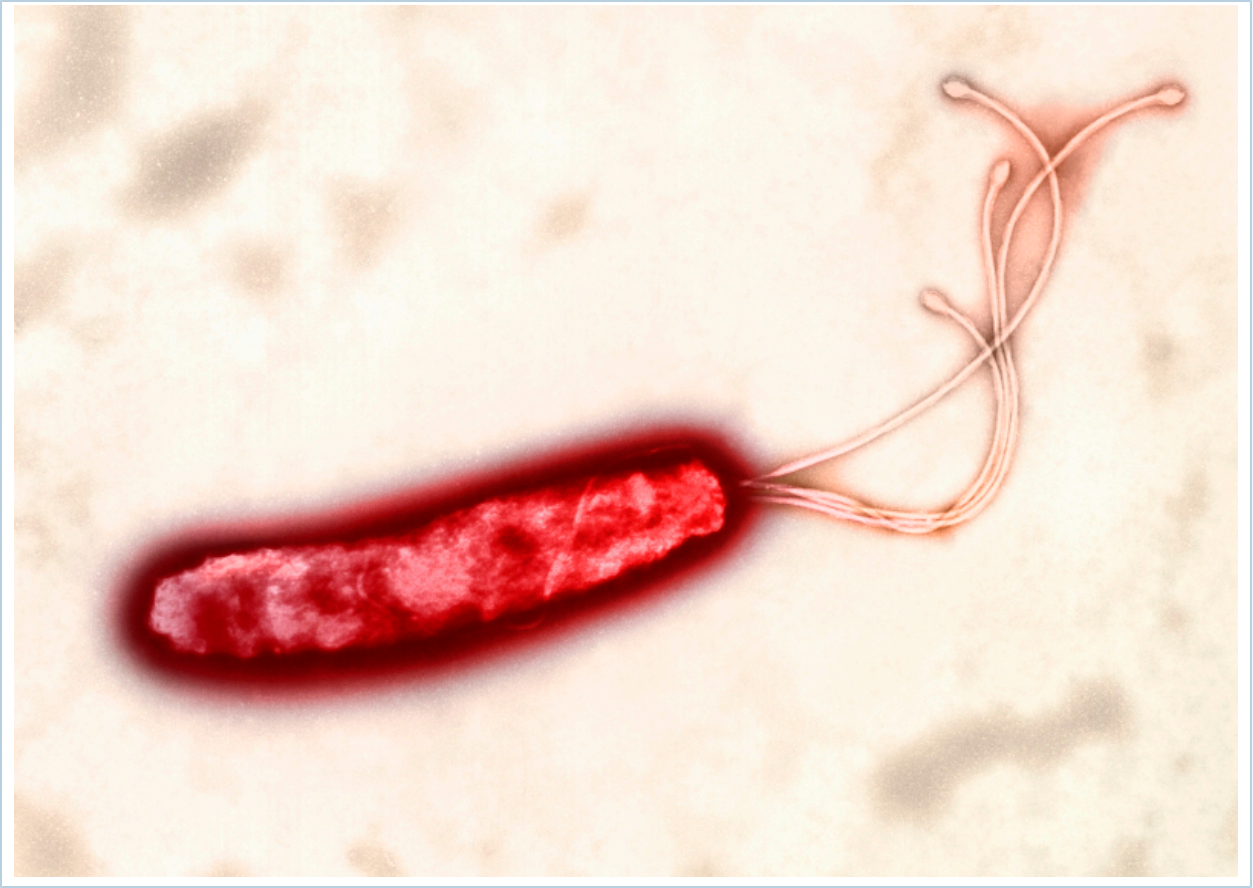
- *H pylori* infection status will normally have been confirmed during the index endoscopy for diagnosis of peptic ulcer, via biopsy samples taken for rapid urease testing or histology.
- If the patient's *H pylori* status is unknown or uncertain after endoscopy, the carbon-13 urea breath test or stool antigen test are the preferred investigations; if these are not available, laboratory-based serology can be used provided its performance has been locally validated.[46] [48] [49][51] [52]

    - The negative predictive value of these tests is >95%. Nonetheless, if a patient with a confirmed peptic ulcer tests negative, a repeat test is warranted.[48]
    - Serology (antibody) testing gives less accurate results than urea breath testing or stool antigen testing and is unable to distinguish between active and historical infection.[46] [53] [54] [55]
    - Proton-pump inhibitors (PPIs), bismuth, or other medications can interfere with the performance of diagnostic tests for *H pylori* .

Leave a 2-week washout period after PPI use and a 4-week washout after antibiotic use before testing for *H pylori* with a breath test or a stool antigen test, as these drugs suppress bacteria and can lead to false negatives.[46] [48]

Re-test to confirm successful eradication of *H pylori* using a carbon-13 urea breath test 6 to 8 weeks after starting treatment.[46]

- There is insufficient evidence to recommend the stool antigen test as a test of eradication.[46]



Helicobacter pylori bacterium, transmission electron micrograph (TEM)
Heather Davies/Science Photo Library

Other investigations

Order a **full blood count** if the patient seems clinically anaemic or has evidence of gastrointestinal bleeding. A raised platelet count may indicate malignancy.

Consider Zollinger-Ellison syndrome in patients with multiple or refractory ulcers, diarrhoea, ulcers distal to the duodenum, or a family history of multiple endocrine neoplasia type 1, and request a fasting serum gastrin level to look for evidence of gastrin hypersecretion. The patient should stop taking any PPI therapy prior to the test.

Also consider the possibility of surreptitious use of NSAIDs if the patient has recurrent or refractory ulcers. This can be detected via urine testing.

History and exam

Key diagnostic factors

abdominal pain (common)

Dyspepsia, a chronic or recurrent abdominal pain or discomfort centred in the upper abdomen, is a common clinical feature.[49]

Commonly related to eating and is often nocturnal.

In patients with duodenal ulcers, pain may be severe and radiate through to back as a result of penetration of the ulcer posteriorly into the pancreas.

presence of risk factors (common)

H pylori infection and chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) are the two strongest risk factors for peptic ulcer disease. About 90% of patients with duodenal ulcers and >70% with gastric ulcers have *H pylori* infection.[17] [19] The incidence of ulcers in chronic NSAID users is about 20% compared with about 5% in non-users.[20] The risk of NSAID-induced ulcers increases with increasing age (>60 years), a history of peptic ulcer, high doses of NSAIDs and longer duration of use, *H pylori* infection, and concurrent use of corticosteroids, bisphosphonates, or other antithrombotic drugs.[21] [22] [23] [24] [25]

Other risk factors include smoking, increasing age, and a personal or family history of peptic ulcer disease.

'pointing sign' (uncommon)

Patient can show site of pain with one finger.

Other diagnostic factors

epigastric tenderness (common)

May occur on palpation of the abdomen.

nausea or vomiting (uncommon)

Nausea is relieved by eating.

Vomiting occurs after eating.

May indicate pyloric stenosis.

early satiety (uncommon)

May indicate pyloric stenosis.

weight loss or anorexia (uncommon)

Patients may experience weight loss or anorexia. Urgent upper gastrointestinal endoscopy (within 2 weeks) is recommended for any patient aged ≥55 years who has weight loss together with any one of dyspepsia, upper abdominal pain, or reflux.[47]

diarrhoea (uncommon)

May indicate Zollinger-Ellison syndrome.

symptoms of anaemia (uncommon)

Gastric and duodenal ulcers may cause iron deficiency anaemia. Symptoms generally include fatigue, pica (abnormal craving or appetite for nonfood substances such as dirt, ice, paint, or clay), and nail changes.

gastrointestinal bleeding (uncommon)

Bleeding may be either occult (stool haem test positive) or overt (haematemesis and/or melaena). This is a complication of peptic ulcer disease.

hypotension or septic#shock (uncommon)

From gastrointestinal bleeding or perforation.

succussion splash (uncommon)

Rarely, a succussion splash may be heard in patients with pyloric stenosis (caused by gastric outlet obstruction).

Investigations

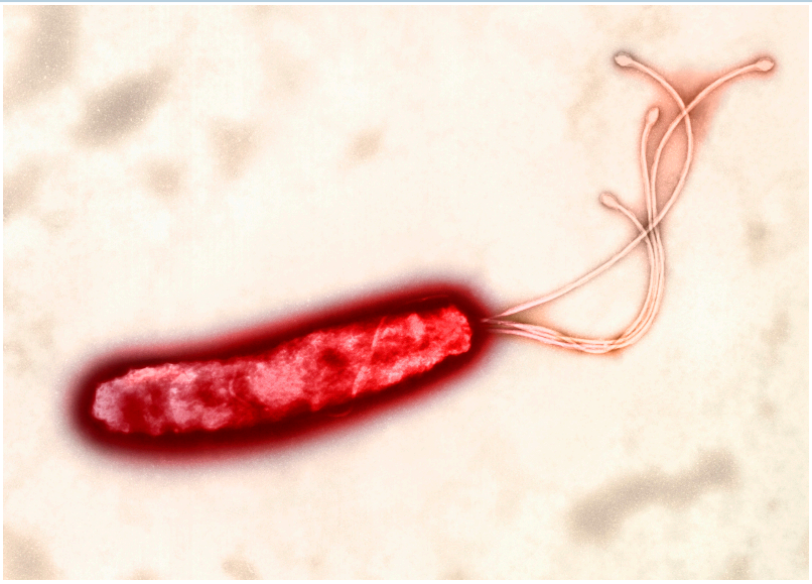
1st test to order

Test	Result
upper gastrointestinal endoscopy Refer any patient who presents with dyspepsia together with significant acute gastrointestinal bleeding, **immediately** (on the same day) to a specialist for endoscopy.[46] Refer any patient ≥55 years who has weight loss together with any one of dyspepsia, reflux, or upper abdominal pain for upper gastrointestinal endoscopy within 2 weeks.[47] Endoscopy is used to exclude malignancy in patients ≥55 years who present with dyspepsia, upper abdominal pain, or reflux together with weight loss, low haemoglobin level, or raised platelet count.[47] Endoscopy is the **definitive diagnostic test** for peptic ulcer disease. It is the most specific and sensitive test. If an ulcer is present, test biopsies for *H pylori* via histology and/or urease testing (rapid urease test). Both tests can detect *H pylori*; however, histology can determine if the ulcer is neoplastic (very rarely) and/or if there is evidence of a non-steroidal anti-inflammatory drug (NSAID) being the likely cause. • Note that in practice, the rapid urease test can be falsely negative if: • There is acute upper gastrointestinal bleeding • The patient is being treated with a PPI • The patient has received antibiotics that might reduce the density of *H pylori* colonisation. Consider endoscopy subsequent to treatment if the patient fails to respond. **Repeat endoscopy after 6 to 8 weeks** in patients with gastric ulcer to ensure ulcer healing and to rule out malignancy (unless excluded at initial endoscopy). Anti-thrombotic treatment with either warfarin or a direct oral anticoagulant (DOAC) or dual antiplatelet therapy is not a contraindication to endoscopy. Upper gastrointestinal endoscopy with or without diagnostic biopsies is regarded as a low-risk procedure for bleeding, and no or minimal alterations in the antithrombotic regimen are required for non-emergency diagnostic endoscopy. • For low-risk endoscopic procedures such as diagnostic endoscopy with or without biopsy, the 2021 update to the British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline on	peptic ulcer; may also detect cause (e.g., *H pylori*)

Test	Result

endoscopy in patients on antiplatelet or anticoagulant therapy recommends:[50]
• Continuing P2Y $_{12}$ receptor antagonists as single or dual antiplatelet therapy (DAPT)
• Continuing warfarin therapy
  • Check international normalised ratio (INR) 1 week before endoscopy
  • If the INR result is within the therapeutic range then continue with the usual daily dose
  • If the INR is above the therapeutic range but <5 then reduce daily dose until INR returns to the therapeutic range
  • If the INR is greater than 5 then defer the endoscopy and contact the anticoagulation clinic, or an appropriate specialist, for advice.
• Omitting the morning dose of DOACs.	

Helicobacter pylori carbon-13 urea breath test or stool antigen test If, after endoscopy, the patient's *H pylori* status is uncertain, establish whether the patient is infected with *H pylori* using the urea breath test or stool antigen test; if these are unavailable, laboratory-based serology can be used provided its performance has been locally validated.[46] [48] • Serology (antibody) testing gives less accurate results than urea breath testing or stool antigen testing and is unable to distinguish between active and historical infection.[46][53][54] [55] Proton-pump inhibitors (PPIs), bismuth, or other medications can interfere with the performance of diagnostic tests for *H pylori* . **Leave a 2-week washout period after PPI use and a 4-week washout after antibiotic use** before testing for *H pylori* with a breath test or a stool antigen test, as these drugs supress bacteria and can lead to false negatives.[46] [48] **Re-test to confirm successful eradication of *H pylori* using a carbon-13 urea breath test 6 to 8 weeks** after starting treatment.[46] • There is insufficient evidence to recommend the stool antigen test as a test of eradication.[46]	positive result if *H pylori* present

Test	Result
 *Helicobacter pylori bacterium, transmission electron micrograph (TEM)* Heather Davies/Science Photo Library	
FBC Order only if the patient seems clinically anaemic or has evidence of gastrointestinal bleeding. • Aids in evaluating the urgency with which the patient requires further work-up, but does not definitively diagnose peptic ulcer disease. • High platelet count or anaemia may indicate malignancy.[47]	microcytic anaemia or high platelet count

Other tests to consider

Test	Result
fasting serum gastrin level Order if there are multiple duodenal ulcers (especially postbulbar) or in a patient with ulcers and diarrhoea. • The patient must be fasting and PPI therapy stopped. Elevated levels in pernicious anaemia and other hypochlorhydric states results in low specificity.	hypergastrinaemia in Zollinger-Ellison syndrome
urine NSAID screen Consider the possibility of surreptitious use of NSAIDs if the patient has recurrent or refractory ulcers.	may be positive

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Oesophageal cancer	• Presence of alarm features (e.g., weight loss, bleeding, anaemia, vomiting, early satiety, or dysphagia, or if the patient develops dyspeptic symptoms after age 55 years), or family history of upper gastrointestinal tract cancer, jaundice, a palpable mass, or lymphadenopathy may be indicative of a gastro-oesophageal neoplasm.	• Distinguished from peptic ulcer disease by endoscopy: shows mass or irregular ulcer. • Diagnosis should be confirmed by endoscopic biopsy. • May require additional imaging to diagnose and stage (e.g., endoscopic ultrasound, CT, MRI).
Stomach cancer	• Presence of alarm features (e.g., weight loss, bleeding, anaemia, vomiting, early satiety, or dysphagia, or if the patient develops dyspeptic symptoms after age 55 years), or family history of upper gastrointestinal cancer, jaundice, a palpable mass, or lymphadenopathy may be indicative of a gastro-oesophageal neoplasm.	• Distinguished from peptic ulcer disease by endoscopy: shows mass or irregular ulcer. • Diagnosis should be confirmed by endoscopic biopsy. • May require additional imaging to diagnose and stage (e.g., endoscopic ultrasound, CT, MRI).
Gastro-oesophageal reflux disease (GORD)	• History of heartburn or pain rising from the lower chest to the throat is typical although not invariable. • May have associated laryngitis, cough, and atypical chest pain.	• Endoscopy shows absence of gastric/duodenal ulcers and, often, erosions in oesophagus. In most patients with pathological acid reflux, the endoscopy is normal. • May require additional testing with ambulatory pH testing to aid in diagnosis.
Gastroparesis	• Early satiety prominent. • A history of longstanding diabetes with evidence of peripheral neuropathy and other end-organ damage.	• Endoscopy may show food stasis. • Definitive diagnosis by gastric emptying study (nuclear medicine imaging).
Biliary colic	• Pain typically in right upper quadrant, about 30 minutes after meals, waxing and waning over minutes or hours.	• Ultrasound or CT scan shows stones in gallbladder and/or bile ducts.

Condition	Differentiating signs / symptoms	Differentiating tests
Acute pancreatitis	• History of gallstones or alcohol use. • Pain typically radiates to back.	• Elevated serum amylase and lipase levels. • CT scan shows inflammation of pancreas.
Non-ulcer dyspepsia (functional dyspepsia)	• Dyspepsia is defined as a discomfort centred in the upper abdomen, commonly related to meals.	• A diagnosis of exclusion after finding no relevant abnormality on appropriate testing.
Coeliac disease	• Diarrhoea and evidence of malabsorption are typical.	• Laboratory testing may show microcytic anaemia, iron deficiency, and low calcium and albumin. • Anti-tissue transglutaminase antibody has sensitivity and specificity of about 95% for the diagnosis. • Endoscopy with duodenal biopsy is the gold standard diagnostic test. Biopsy shows flattening of the villi.
Irritable bowel syndrome	• Pain may be indistinguishable from that of peptic ulcer disease, but alteration of bowel habit separates this syndrome. • Bloating is a common complaint.	• A diagnosis of exclusion after finding no relevant abnormality on appropriate testing.
Pleuritic pain	• Chest pain altered by respiration.	• Chest x-ray may reveal pneumonia or effusion.
Pericarditis	• Constant pleuritic central chest pain that is worse in the recumbent position and radiates to one or both trapezius ridges. • History of transmural myocardial infarction, cardiac surgery, neoplasm, viral and bacterial infection, uraemia, dialysis treatment, or systemic autoimmune disorders may be present. • A prodrome of myalgias and malaise may be present with any cause of acute pericarditis, particularly in young adults. High or spiking fever may also be present. • Pericardial friction rub heard on examination. The rub, when present, is described	• ECG shows upwards concave ST-segment elevation globally with PR depressions. • Serum troponin is mildly elevated. • Chest x-ray may be normal or show a water bottle-shaped enlarged cardiac silhouette. • C-reactive protein, erythrocyte sedimentation rate (ESR), and white blood cells are usually elevated.

Condition	Differentiating signs / symptoms	Differentiating tests
	as high-pitched or squeaky. It is heard best at the left sternal edge with the patient leaning forwards at end-expiration.	

Recommendations

Key Recommendations

Acute upper gastrointestinal bleeding from a peptic ulcer requires urgent evaluation.

- Use the Blatchford risk score at first assessment to predict the need for intervention[56] [57] [58] [59]
- Transfuse any patient with massive bleeding with blood, platelets and clotting factors in line with local protocols.[56] [60]
- Arrange therapeutic (and diagnostic) endoscopy on the same day for patients presenting with dyspepsia and significant acute gastrointestinal bleeding.[56] [59]
- **Prescribe proton-pump inhibitors** (PPIs) to patients with a bleeding ulcer who have signs of recent haemorrhage visible at endoscopy.[56] [59] [61]

For patients who are ***Helicobacter pylori*** **negative** and have peptic ulcer disease (without active bleeding):[46]

- Stop non-steroidal anti-inflammatory drugs (NSAIDs) where possible.
- Start full-dose ulcer healing therapy for 8 weeks.

For patients who are ***H pylori*** **positive** and have peptic ulcer disease (without active bleeding):[46]

- If the patient is **not** a long-term user of NSAIDs:
    - Offer a 7-day course of *H pylori* eradication therapy, in line with NICE recommendations.[46]
    - Consider offering ulcer healing therapy with a full-dose PPI or H2 antagonist for 8 weeks.
        - This is standard practice in the UK based on clinical experience but bear in mind that ulcer healing therapy is not specifically recommended for this group by NICE.

- If the patient **is** a long-term user of NSAIDs:
    - Stop NSAIDs where possible[46]
    - NICE recommends to:
        - Start with an 8-week course of ulcer healing therapy (with a full-dose PPI or H2 antagonist).[46]
        - Then offer *H pylori* eradication therapy (typically a 7-day course of triple therapy [PPI + two antibiotics]).[46]

- If the patient has a family history of gastric cancer, *H pylori* eradication is associated with a reduced risk of gastric cancer.[62]
    - Offer *H pylori* eradication therapy (typically a 7-day course of triple therapy).

- Be aware that ulcer healing therapy and eradication therapy are sequential treatments. In practice, a specialist may advise eradication therapy before ulcer healing therapy or vice-versa based on their clinical experience and preference.
- **Re-test** (with a urea breath test) any initially *H pylori* positive patient 6 to 8 weeks after beginning eradication treatment, depending on the size of the lesion.[46]
    - Leave a 2-week washout period after PPI use and a 4-week washout after antibiotic use before re-testing for *H pylori* as these drugs suppress bacteria and can lead to false negatives.[46] [48]
- **Re-treat** patients who are still *H pylori* positive with at least one second-line eradication therapy regimen.[46][63]
- **Repeat endoscopy** in patients with gastric ulcer and *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46]

Consider specialist referral for any patient with:[46]

- Unexplained, or treatment-resistant gastro-oesophageal symptoms
- *H pylori* that has not responded to second-line eradication therapy.

Full Recommendations

Treatment goals

The goals of therapy are to:

- Treat complications (e.g., active bleeding)
- Determine and eliminate the underlying cause whenever possible - most commonly *H pylori* infection and/or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs)
- Relieve symptoms
- Heal ulcers.

Actively bleeding ulcer

Active gastrointestinal bleeding requires urgent evaluation with resuscitation and supportive care as appropriate.[64]

Peptic ulcer is the most common cause of life-threatening acute gastrointestinal bleeding, accounting for around 35% of cases.[56] Use the following formal risk assessment scores for any patient with acute upper gastrointestinal bleeding:[56]

- The **Blatchford score** at first assessment to predict the need for intervention[57] [58] [59]
- The full **Rockall score** after endoscopy to estimate the risk of rebleeding or death.[65]

Transfuse any patient with massive bleeding with blood, platelets, and clotting factors in line with local protocols for managing massive bleeding.[56] [60]

- The British Society of Gastroenterology (BSG) care bundle for acute upper gastrointestinal bleeding recommends giving:[64]
    - Red blood cell transfusion if the patient's haemoglobin is <70 g/L, with a target of 70 to 100 g/L
    - Platelets if the patient's platelet count is ≤50 × 10^9 /L.

Do not use tranexamic acid to treat patients with acute gastrointestinal bleeding.[60] [66] [67]

- Evidence from the HALT-IT trial, in which more than 12,000 patients with severe gastrointestinal bleeding were randomised to tranexamic acid or placebo, showed no improvement in outcomes but increased adverse effects for those who received tranexamic acid.[66] [67] [Evidence B]
- A further systematic review and meta-analysis of extended-use high-dose tranexamic acid failed to show any improvement in mortality or bleeding outcomes.[67] [68]

For further information, see:

- Assessment of upper gastrointestinal bleeding
- Shock .

Endoscopic management of bleeding

Following resuscitation, patients with severe acute upper gastrointestinal bleeding should undergo upper gastrointestinal endoscopy within 24 hours.[59] [69] [70] [71]

Very early (less than 6 hours from presentation) endoscopy has not been associated with improved patient outcomes, and in some cases can worsen outcome.[59] [69] [70] [71]

Most ulcer bleeding can be treated endoscopically to achieve haemostatic control.

Use one of the following methods to achieve haemostatic control of an actively bleeding ulcer:[56] [59]

- A mechanical method (e.g., clips) with adrenaline (epinephrine)
- Thermal coagulation with adrenaline[59] [72]
- Fibrin or thrombin with adrenaline.

For an ulcer with a non-bleeding visible vessel use:

- A mechanical method, thermal coagulation, or fibrin/thrombin as monotherapy or in combination with adrenaline.

Options for persistent refractory bleeding include:

- Cap-mounted clips - have been shown to be at least as effective as other more traditional modalities (such as thermal coagulation) for primary haemostasis of peptic ulcer bleeding and are particularly useful for rescue therapy or large (>20 mm) or fibrotic ulcers, or those with a large

visible vessel (>2 mm) or located in a high-risk vascular area (e.g., gastroduodenal, left gastric arteries)[59] [73] [74]
- Haemostatic sprays for rescue therapy of uncontrolled bleeding (not for primary haemostasis due to a higher rate of rebleeding than with more definitive methods).[75] [76]

Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.[56] [59] [72]

After endoscopy, prescribe PPI therapy to any patient who had endoscopic evidence of recent haemorrhage.[56][59] [61] Some centres use a high-dose oral PPI, but the standard approach remains an intravenous infusion for 72 hours, followed by a switch to oral administration.[61]

The role of pre-endoscopic PPI therapy in patients who present with ulcer bleeding remains an area of ongoing debate.[56] [77] The UK National Institute for Health and Care Excellence (NICE) recommends that acid-suppression drugs (i.e., PPIs or H2 antagonists) should **not** be offered **before** endoscopy because of a lack of evidence to show improved outcomes.[56] International consensus recommendations state that pre-endoscopic PPI therapy can be considered on the basis that it may downstage the lesion or reduce the need for endoscopic haemostatic treatment, although it should not delay endoscopy.[77] [78]

If the patient **re-bleeds** after their initial endoscopy:

- Repeat the endoscopy if the patient is stable and treat endoscopically or with emergency surgery.[56] [61]
- Offer interventional radiology if the patient is unstable.[56] [61]
    - Refer urgently for surgery if interventional radiology is not promptly available.[56] [61]

Patients taking anticoagulation therapy (e.g., warfarin, direct oral anticoagulants [DOACs])

Consider seeking advice from an appropriate **specialist** if the patient is taking warfarin or a DOAC.

- The BSG consensus care bundle for acute upper gastrointestinal bleeding and the 2021 update to the BSG and European Society of Gastrointestinal Endoscopy (ESGE) guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommend:[64] [50]
    - Suspending DOACs at presentation and seeking advice from a haematologist when managing patients with severe haemorrhage to weigh up the risks and benefits of the DOAC.
    - Suspending warfarin at presentation.
        - The BSG consensus care bundle stresses the importance of ensuring a plan is in place for restarting warfarin.[64] Consult a specialist to discuss the risks associated with stopping warfarin and the need for monitoring.[64] [50]
- In haemodynamically unstable patients, the 2021 update to the BSG and ESGE guideline recommends:[50]

- In patients who are taking warfarin, give intravenous vitamin K and four-factor prothrombin complex concentrate. Fresh frozen plasma can be used if prothrombin complex concentrate is not available.
- If the patient is taking a DOAC, consider the use of reversal agents: idarucizumab in patients taking dabigatran, and andexanet alfa in patients taking anti-factor-Xa. Intravenous four-factor prothrombin complex concentrate can be used if andexanet alfa is not available.

- Note that the UK National Institute for Health and Care Excellence (NICE) recommends:[56]
  - Prothrombin complex concentrate in patients who are taking warfarin and actively bleeding
  - Following local warfarin protocols to treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped
  - Recombinant factor VIIa (eptacog alfa) when all other methods have failed.

If any medications are temporarily stopped, also seek advice on the appropriate time for these to be re-started. The 2021 update to the BSG and ESGE guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommends restarting anticoagulation:[50]

- As soon as possible after 7 days of anticoagulant interruption in patients with low thrombotic risk
- Preferably within 3 days of anticoagulant interruption in patients with high thrombotic risk, with heparin bridging.

Patients taking aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or dual antiplatelet therapy

If the patient is taking aspirin, other NSAIDs (including cyclo-oxygenase-2 [COX-2] inhibitors), or dual antiplatelet therapy:

- In general, **continue aspirin with gastroprotection** in the acute phase, if your patient is taking this for **secondary prevention**.[50] [56] [59] [64][79]
  - Consider seeking urgent advice from a specialist if there is major haemorrhage.
    - NICE doesn't make a specific recommendation about major haemorrhage, but advises continuing aspirin only once haemostasis has been achieved.[56]
    - The BSG consensus care bundle for acute upper gastrointestinal bleeding and the 2021 update to the BSG and ESGE guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommend continuing aspirin if this is taken as part of dual antiplatelet therapy with a $P2Y_{12}$ inhibitor (e.g., clopidogrel, prasugrel, or ticagrelor), and the $P2Y_{12}$ is temporarily stopped.[50] [64]
    - The 2021 update to the BSG and ESGE guideline recommends that, if aspirin is stopped, it should be restarted as soon as haemostasis is achieved or there is no further evidence of haemorrhage.[50]

- The BSG care bundle cites two studies that demonstrate a three-fold increase in the risk of cardiovascular or cerebrovascular events if aspirin, prescribed for secondary prevention, is discontinued.[50] [64][79] [80] [81]

- The 2021 update to the BSG and ESGE guideline recommends considering permanently discontinuing aspirin if the patient is taking it for **primary prevention**.[50]
- If the patient is taking any **other NSAIDs** (including COX-2 inhibitors), NICE recommends stopping these during the acute phase.[50]
- If the patient is taking dual antiplatelet therapy, **seek advice from the appropriate specialist** to weigh up the benefits and risks of continuing the **P2Y $_{12}$ inhibitor**. Discuss the balance of benefits versus risk with your patient. In general, if the patient:[64]

    - Does not have coronary artery stents, the P2Y $_{12}$ inhibitor should be stopped temporarily until haemostasis is achieved
    - Does have coronary artery stents, dual antiplatelet therapy should ideally be continued due to the high risk of stent thrombosis. However, the risks and benefits of doing so need to be carefully considered by a specialist.

If the ulcer is recurrent or resistant to treatment, the multidisciplinary specialists involved in the patient's care should balance the risks and benefits of continued antiplatelet therapy.

After intervention to stop the bleeding, investigate the presence of *H pylori* and treat according to the guidelines for patients with no active bleeding.

Ulcer with no active bleeding

Treatment is aimed at determining and eliminating the underlying cause, together with ulcer healing therapy. The major causative factors responsible for peptic ulceration are the use of NSAIDs and infection with *H pylori.* Determine the presence of *H pylori* because treatment is based on whether the patient is *H pylori* positive or negative.

H pylori negative

H pylori negative ulcers, the majority of which are associated with use of NSAIDs, are increasingly commonly seen, owing to a decline in prevalence of *H pylori* .[82]

For patients on NSAIDs with a diagnosed peptic ulcer, stop the NSAID where possible.[46]

- If this is not possible, and in people at high risk (previous ulceration), consider a COX-2 inhibitor instead of a standard NSAID and prescribe a PPI.[46]

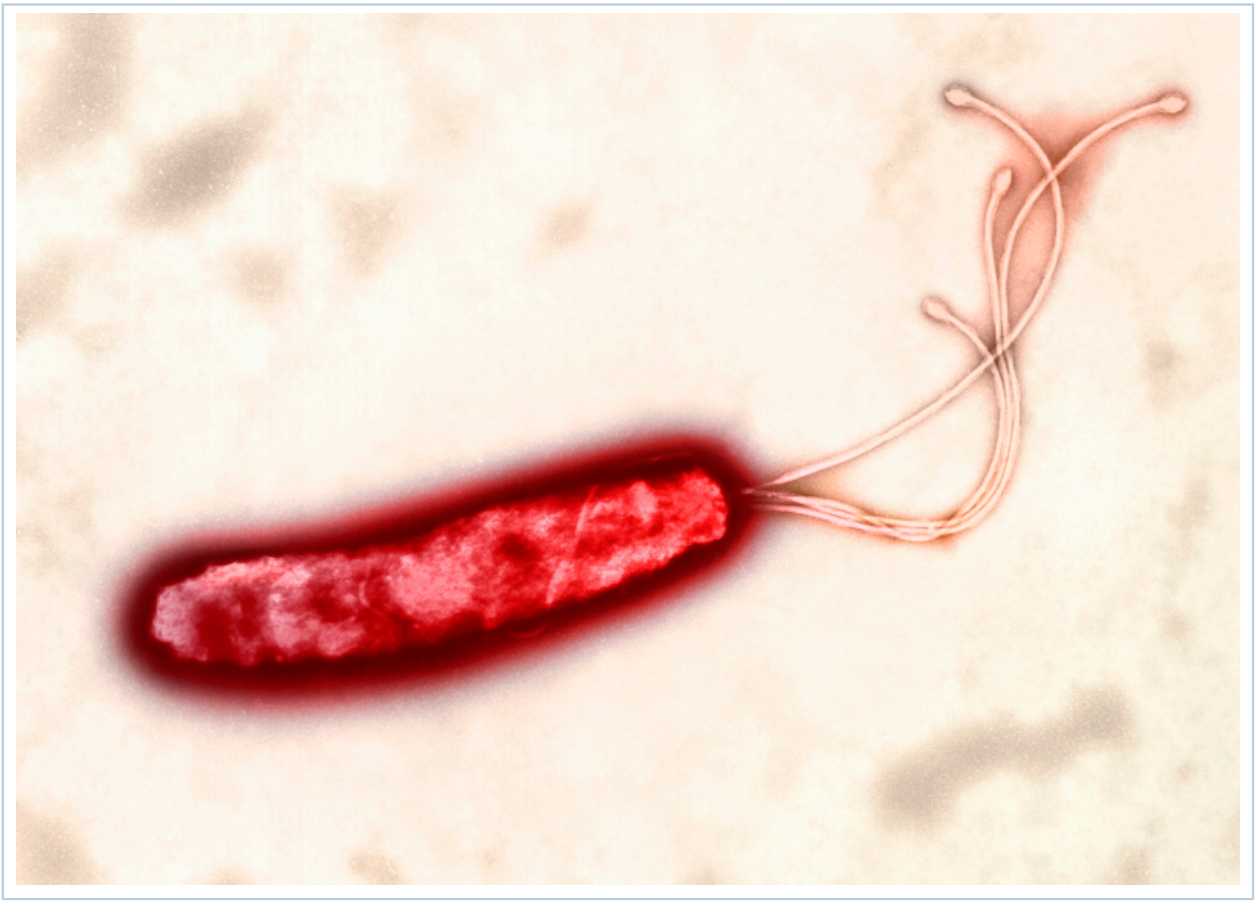
Start ulcer healing therapy.

- Offer full-dose PPI therapy for 4 to 8 weeks to patients who are *H pylori* negative.[46]
- H2 antagonists may be used if the patient is unresponsive to a PPI.[46]
- Antacids are relatively ineffective and slow to produce healing and are not recommended.

Adverse effects of PPI therapy include diarrhoea, nausea, and modest increases in gastrin levels. They may also mask the symptoms of gastric cancer.

- If diarrhoea develops, consider Crohn's disease, Zollinger-Ellison syndrome, microscopic colitis (lymphocytic or collagenous colitis) and more rarely, *Clostridium difficile* -associated disease. Review the need for treatment.[48]

H pylori positive



Helicobacter pylori bacterium, transmission electron micrograph (TEM)

Heather Davies/Science Photo Library

If the *H pylori* positive patient **is not a long-term user of NSAIDs**:

- Offer a 7-day course of *H pylori* eradication therapy.[46]
  - This is in line with recommendations from the UK National Institute for Health and Care Excellence (NICE).[46]
- Consider offering ulcer healing therapy with a full-dose PPI or H2 antagonist for 8 weeks
  - This is standard practice in the UK based on clinical experience but bear in mind that ulcer healing therapy is not specifically recommended for this group by NICE.

If the *H pylori* positive patient **is a long-term user of NSAIDs (or low-dose aspirin)**:[46]

- Discontinue any NSAID the patient is taking, if possible.[46] If this is not possible, and in people at high risk (previous ulceration), consider a COX-2 inhibitor instead of a standard NSAID and prescribe a PPI.[46]
    - Weigh up the benefits versus risks of reducing or stopping any other potential ulcer-inducing drugs, including aspirin.[83] Seek senior/specialist advice if low-dose aspirin is being taken for secondary prevention of cardiovascular or cerebrovascular events as the benefits of continuing may need to take priority.[79]
- NICE recommends to:
    - Start with ulcer healing therapy with a full-dose PPI or H2 antagonist for 8 weeks.[46]
    - Then offer *H pylori* eradication therapy (typically a 7-day course of triple therapy [PPI + two antibiotics]).[46] See *H pylori eradication therapy* below.

Be aware that ulcer healing therapy and eradication therapy are sequential treatments. In practice, a specialist may advise eradication therapy before ulcer healing therapy or vice-versa based on their clinical experience and preference. Always follow your local protocols and use your clinical judgment to determine the optimal approach for your individual patient.

H pylori eradication therapy

Eradication therapy leads to ulcer healing and a dramatic decrease in ulcer recurrence.[84] Most regimens are 70% to 90% efficacious in practice, limited mainly by antibiotic resistance or patient adherence to the regimen. Delayed clearance of *H pylori* is associated with a higher rate of subsequent upper gastrointestinal bleeding.[85]

- Check the patient's antibiotic history, ascertain antibiotic allergy status, and stress the importance of adherence.

Eradication regimens vary between guidelines and locations; traditional empirical 'triple therapies' rarely achieve satisfactory eradication rates, and success rates vary according to local and regional resistance patterns.[86] Empirical therapies should be restricted to those shown to be highly effective locally.[53] [86] [87]

The UK's National Institute for Health and Care Excellence (NICE) and Public Health England (PHE) make specific recommendations on treatment regimens, but note that these will often need to be substituted with local protocols that take account of resistance patterns because traditional empirical 'triple therapies' often fail to achieve successful eradication:[46] [48]

- First-line triple therapy for 7 days with a course of a PPI plus two antibiotics; NICE and PHE recommend amoxicillin plus either clarithromycin or metronidazole. Alternative regimens are outlined for people who are penicillin-allergic or who have had previous clarithromycin exposure.
- Other guidelines recommend alternative approaches: for example, the European guidelines recommend bismuth quadruple therapy (a PPI, bismuth, tetracycline, and metronidazole) as initial treatment.[53]

Recurrent or refractory ulcers

For patients who continue to take NSAIDs after a peptic ulcer has healed, discuss the potential harm associated with NSAIDs.[46]

- Review the need for NSAID use regularly (at least every 6 months)
- Offer a trial of NSAID use on a limited 'as needed' basis[46]
- Consider:[46]
    - Reducing the NSAID dose
    - Substituting the NSAID with paracetamol
    - Using an alternative analgesic
    - Using low-dose ibuprofen.

In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a **COX-2 inhibitor** instead of a standard NSAID. In either case, prescribe with a PPI.[46]

In people with an unhealed ulcer, exclude non-adherence, malignancy, failure to detect *H pylori*, inadvertent or surreptitious NSAID use, other ulcer-inducing medication, and rare causes such as Zollinger–Ellison syndrome or Crohn's disease.[46]

If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms.[46]

- Encourage patients to manage their own symptoms by using PPI treatment on an 'as-needed' basis.[46]
- Offer H2 antagonist therapy if there is an inadequate response to a PPI.[46]

Long-term maintenance acid-suppression therapy may be used in selected high-risk patients (e.g., frequent recurrences, large or refractory ulcers) with or without *H pylori* infection. The preferred regimen and duration of therapy is uncertain, although most clinicians use a PPI.

Safety of long-term PPI therapy

PPIs are an effective treatment for peptic ulcer disease.[45] Concerns exist, however, over their long-term use.

- Retrospective analyses suggest an association between PPI use and osteoporosis, pneumonia, dementia, stroke, and all-cause mortality.[88] [89] [90] [91] [92] [93] [94] However, these studies are unable to establish a causal relationship.[95]
- A prospective analysis of more than 200,000 participants in three big studies, over a combined 2.1 million person-years of follow-up, found that regular use of PPIs was associated with a higher risk of developing type 2 diabetes (HR 1.24, 95% CI 1.17 to 1.31). The risk of diabetes increased with duration of PPI use.[96]
- In possibly the largest prospective randomised PPI trial for any indication (n=17,958 patients with cardiovascular disease), no significant difference in adverse effects was reported between pantoprazole and placebo at 3 years (53,000 patient years of follow-up), aside from a possible increase in enteric infection.[97]

- One smaller prospective, multicentre double-blind study, including 115 healthy post-menopausal women, found that 26 weeks of treatment with a PPI had no clinically meaningful effects on bone homeostasis.[98]
- A systematic review and meta-analysis that included more than 600,000 patients found no relationship between the use of PPIs and increased risk of dementia.[99] This was also the conclusion in another meta-analysis of just over 200,000 patients, where no clear evidence was found to suggest an association between PPI use and risk of dementia.[100]
- A cohort study of more than 700,000 patients in the UK showed an association between PPI use and all-cause mortality.[94] However, significant confounding effects mean that conclusions about causality cannot be made.[94]
- PPIs are associated with changes in the microbiome. The clinical significance of these changes is uncertain.[101]

PPIs should only be prescribed for appropriate indications and should be limited to the warranted therapeutic duration of therapy. Based on current data, the overall benefits of PPI treatment outweigh the potential risks in most patients.

Drug safety alert: Adverse events associated with long-term use of PPIs

Concerns exist over the long-term use of PPIs.

Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs, rarely after 3 months, but usually after 1 year of treatment. Serious features of hypomagnesaemia include fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia. Hypomagnesaemia usually improves after magnesium replacement and discontinuation of the PPI.[102]

PPIs have been associated with an increased risk of **osteoporosis** and a modest increase in the risk of hip, wrist, or spine fracture, especially if used by older people in high doses and for >1 year.[103]

PPIs have been linked rarely, but probably causally, to **subacute cutaneous lupus erythematosus** (SCLE).[104]

In being vigilant for these rare adverse events:

- Consider measuring magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who take concomitant digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics).[102]
- Treat patients at risk of osteoporosis according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.[103]
- Advise patients who develop arthralgia and skin lesions in sun-exposed areas to avoid sunlight, and consider giving topical or systemic corticosteroids if there are no signs of remission after a few weeks or months.[104]
- Consider stopping the PPI unless it is imperative for a serious acid-related condition.
- Take into account any use of PPIs obtained over-the-counter.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

active bleeding ulcer		
	1st	**urgent evaluation ± blood transfusion**
	plus	**endoscopy**
	consider	**proton-pump inhibitor (PPI)**
	2nd	**repeat endoscopy or embolisation via interventional radiology or surgery**
no active bleeding: Helicobacter pylori negative		
	1st	**treat underlying cause plus proton-pump inhibitor (PPI)**
	2nd	**H2 antagonist**
no active bleeding: Helicobacter pylori positive		
no long-term use of non-steroidal anti-inflammatory drugs or low-dose aspirin	**1st**	**H pylori eradication therapy**
	consider	**ulcer healing therapy**
	2nd	**alternative H pylori eradication regimen**
	3rd	**referral to specialist service**
with long-term use of non-steroidal anti-inflammatory drugs or low-dose aspirin	**1st**	**ulcer healing therapy**
	plus	**H pylori eradication therapy**
	2nd	**alternative H pylori eradication regimen**
	3rd	**referral to specialist service**

Ongoing (summary)

recurrent or refractory ulcers		
	1st	**long-term acid suppression therapy**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

active bleeding ulcer

1st **urgent evaluation ± blood transfusion**

» Active gastrointestinal bleeding requires urgent evaluation, with resuscitation and supportive care as appropriate.[64]

» For any patient with acute upper gastrointestinal bleeding, use the **Blatchford score** at first assessment to predict the need for intervention.[56] [57] [58] [59]

» Transfuse any patient with massive bleeding with blood, platelets, and clotting factors in line with local protocols.[56] [60]

- The British Society of Gastroenterology (BSG) care bundle for acute upper gastrointestinal bleeding recommends giving:[64]
  - Red blood cell transfusion if the patient's haemoglobin is <70 g/L, with a target of 70 to 100 g/L
  - Platelets if the patient's platelet count is ≤50 × 10^9 /L.

» **Patients taking anticoagulation therapy (e.g., warfarin, direct oral anticoagulants [DOACs])**

» Consider seeking advice from an appropriate **specialist** if the patient is taking warfarin or a DOAC.

- The BSG consensus care bundle for acute upper gastrointestinal bleeding and the 2021 update to the BSG and European Society of Gastrointestinal Endoscopy (ESGE) guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommend:[50] [64]
  - Suspending DOACs at presentation and seeking advice from a haematologist when managing patients with severe haemorrhage

Acute

to weigh up the risks and benefits of the DOAC
- Suspending warfarin at presentation.
    - The BSG consensus care bundle stresses the importance of ensuring a plan is in place for restarting warfarin.[64] Consult a specialist to discuss the risks associated with stopping warfarin and the need for monitoring.[50] [64]

- In haemodynamically unstable patients, the 2021 update to the BSG and ESGE guideline recommends:[50]
    - In patients who are taking warfarin, give intravenous vitamin K and four-factor prothrombin complex concentrate. Fresh frozen plasma can be used if prothrombin complex concentrate is not available.
    - If the patient is taking a DOAC, consider the use of reversal agents: idarucizumab in patients taking dabigatran, and andexanet alfa in patients taking anti-factor-Xa. Intravenous four-factor prothrombin complex concentrate can be used if andexanet alfa is not available.

- Note that the UK National Institute for Health and Care Excellence (NICE) recommends:[56]
    - Prothrombin complex concentrate in patients who are taking warfarin and actively bleeding
    - Following local warfarin protocols to treat patients who are taking warfarin and whose upper gastrointestinal bleeding has stopped

Acute

- Recombinant factor VIIa (eptacog alfa) when all other methods have failed.

» If any medications are temporarily stopped, also seek advice on the appropriate time for these to be re-started. The 2021 update to the BSG and ESGE guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommends restarting anticoagulation:[50]

- As soon as possible after 7 days of anticoagulant interruption in patients with low thrombotic risk.
- Preferably within 3 days of anticoagulant interruption in patients with high thrombotic risk, with heparin bridging.

» Patients taking aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or dual antiplatelet therapy

» If the patient is taking aspirin, other NSAIDs (including cyclo-oxygenase-2 [COX-2] inhibitors), or dual antiplatelet therapy:

- In general, **continue aspirin** in the acute phase, if your patient is taking this for **secondary prevention**.[50] [56] [59] [64] [79]
  - Consider seeking urgent advice from a specialist if there is major haemorrhage.
    - The National Institute for Health and Care Excellence (NICE) doesn't make a specific recommendation about major haemorrhage, but advises continuing aspirin only once haemostasis has been achieved.[56]
- The BSG consensus care bundle for acute upper gastrointestinal bleeding and the 2021 update to the BSG and ESGE guideline on endoscopy in patients on antiplatelet or anticoagulant therapy recommend continuing aspirin if this is taken as part of dual antiplatelet therapy

Acute

with a P2Y $_{12}$ inhibitor (e.g., clopidogrel, prasugrel, or ticagrelor), and the P2Y $_{12}$ is temporarily stopped.[50][64] However, the 2021 update to the BSG and ESGE guideline recommends that, if aspirin is stopped, it should be restarted as soon as haemostasis is achieved or there is no further evidence of haemorrhage.[50]

- The BSG care bundle cites two studies that demonstrate a three-fold increase in the risk of cardiovascular or cerebrovascular events if aspirin, prescribed for secondary prevention, is discontinued.[64] [79] [80] [81]

- The 2021 update to the BSG and ESGE guideline recommends considering permanently discontinuing aspirin if the patient is taking it for **primary prevention**.[50]
- If the patient is taking any **other NSAIDs** (including COX-2 inhibitors), NICE recommends stopping these during the acute phase.[50]
- If the patient is taking dual antiplatelet therapy, **seek advice from the appropriate specialist** to weigh up the benefits and risks of continuing the **P2Y $_{12}$ inhibitor**. Discuss the balance of benefits versus risk with your patient. In general, if the patient:[64]
  - Does not have coronary artery stents, the P2Y $_{12}$ inhibitor should be stopped temporarily until haemostasis is achieved
  - Does have coronary artery stents, dual antiplatelet therapy should ideally be continued due to the high risk of stent thrombosis. However, the risks and benefits of doing so need to be carefully considered by a specialist.

» If the ulcer is recurrent or resistant to treatment, the multidisciplinary specialists involved in the patient's care should balance the risks and benefits of continued antiplatelet therapy.

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» Do not use tranexamic acid to treat patients with acute gastrointestinal bleeding.[66] [67]

- Evidence from the HALT-IT trial, in which more than 12,000 patients with severe gastrointestinal bleeding were randomised to tranexamic acid or placebo, showed no improvement in outcomes but increased adverse effects for those who received tranexamic acid.[66] [67]

» For further information, see:

- Assessment of upper gastrointestinal bleeding
- Shock .

plus endoscopy

Treatment recommended for ALL patients in selected patient group

» Most bleeding from peptic ulcers can be treated endoscopically. Endoscopy aids in confirming the diagnosis and identifying the cause of bleeding, as well as stopping the bleeding.

- Following resuscitation, patients with severe acute upper gastrointestinal bleeding should undergo upper gastrointestinal endoscopy within 24 hours.[59] [69] [70] [71]
- Very early (less than 6 hours from presentation) endoscopy has not been associated with improved patient outcomes, and in some cases can worsen outcome.[59] [69] [70] [71]

» Use one of the following methods to achieve haemostatic control of an actively bleeding ulcer:[56] [59]

- A mechanical method (e.g., clips) with adrenaline (epinephrine)
- Thermal coagulation with adrenaline[59] [72]
- Fibrin or thrombin with adrenaline.

» For an ulcer with a non-bleeding visible vessel use:

- A mechanical method, thermal coagulation, or fibrin/thrombin as

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monotherapy or in combination with adrenaline.

» Options for persistent refractory bleeding include:

- Cap-mounted clips - have been shown to be at least as effective as other more traditional modalities (such as thermal coagulation) for primary haemostasis of peptic ulcer bleeding and are particularly useful for rescue therapy or large (>20 mm) or fibrotic ulcers, or those with a large visible vessel (>2 mm) or located in a high-risk vascular area (e.g., gastroduodenal, left gastric arteries)[59] [73] [74]
- Haemostatic sprays for rescue therapy of uncontrolled bleeding (not for primary haemostasis due to a higher rate of rebleeding than with more definitive methods).[75] [76]

» Do not use adrenaline as monotherapy for the endoscopic treatment of non-variceal upper gastrointestinal bleeding.[56]

» After endoscopy, assess for the presence of *Helicobacter pylori* and treat the patient according to the guidelines for patients with no active bleeding.

» Use the full **Rockall score** after endoscopy to estimate the risk of rebleeding or death.[65]

» If the patient **re-bleeds** after their initial endoscopy, repeat the endoscopy and treat endoscopically or with emergency surgery.[56]

consider **proton-pump inhibitor (PPI)**

Treatment recommended for SOME patients in selected patient group

Primary options

» omeprazole: 80 mg intravenously initially over 40-60 minutes, followed by 8 mg/hour intravenous infusion for 72 hours, then switch to oral therapy

OR

» esomeprazole: 80 mg intravenously initially over 30 minutes, followed by 8 mg/hour intravenous infusion for 72 hours, then switch to oral therapy

Acute

» **After endoscopy**, prescribe a PPI to any patient who had endoscopic evidence of recent haemorrhage.[56] [61] Some centres use a high-dose oral PPI, but the standard approach remains an intravenous infusion for 72 hours, followed by a switch to oral administration.[61] In practice, continue the PPI for 6 to 8 weeks irrespective of *H pylori* status. If on long-term NSAID or aspirin, with no way of stopping this, continue long-term PPI prophylaxis.

» The role of **pre-endoscopic** PPI therapy in patients who present with ulcer bleeding remains an area of ongoing debate.[56] [77] The UK National Institute for Health and Care Excellence (NICE) recommends that acid-suppression drugs (i.e., PPIs or H2 antagonists) should **not** be offered **before** endoscopy because of a lack of evidence to show improved outcomes.[56] International consensus recommendations state that pre-endoscopic PPI therapy can be considered on the basis that it may downstage the lesion or reduce the need for endoscopic haemostatic treatment, although it should not delay endoscopy.[77]

2nd **repeat endoscopy or embolisation via interventional radiology or surgery**

» If the patient **re-bleeds** after their initial endoscopy, options include:

- Repeating the endoscopy and treating endoscopically if the patient is stable[61]
- Offering interventional radiology to any unstable patient who re-bleeds after endoscopic treatment[56] [61]
- Referring urgently for surgery if interventional radiology is not promptly available.[56]

no active bleeding: Helicobacter pylori negative

1st **treat underlying cause plus proton-pump inhibitor (PPI)**

Primary options

» esomeprazole: 20 mg orally once daily

OR

» lansoprazole: 30 mg orally once daily

OR

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» omeprazole: 20 mg orally once daily

OR

» pantoprazole: 40 mg orally once daily

OR

» rabeprazole: 20 mg orally once daily

» For patients on non-steroidal anti-inflammatory drugs (NSAIDs) with a diagnosed peptic ulcer, stop the NSAID where possible.

» Start ulcer healing therapy.

- Offer full-dose PPI therapy for 4 to 8 weeks to patients who are *H pylori* negative.[46]

» **Adverse effects** of PPI therapy include diarrhoea, nausea, and modest increases in gastrin levels. They may also mask the symptoms of gastric cancer.

- If diarrhoea develops, consider Crohn's disease, Zollinger-Ellison syndrome, microscopic colitis (lymphocytic or collagenous colitis) and, more rarely, *Clostridium difficile* -associated disease. Review the need for treatment.[48]

» Treatment course: 4 to 8 weeks.

2nd **H2 antagonist**

Primary options

» famotidine: 40 mg orally once daily at night

OR

» nizatidine: 300 mg orally once daily at night

» Consider using an H2 antagonist (e.g., famotidine, nizatidine) if the patient is unresponsive to a PPI.[46]

- H2 antagonists are less effective than PPIs, but induce healing in the majority of patients.[105]

» Treatment course: 4 to 8 weeks.

no active bleeding: Helicobacter pylori positive

Acute

no long-term use of non-steroidal anti-inflammatory drugs or low-dose aspirin

1st **H pylori eradication therapy**

Primary options

No penicillin allergy

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily

--AND--

» amoxicillin: 1000 mg orally twice daily

--AND--

» clarithromycin: 500 mg orally (immediate-release) twice daily
-or-
» metronidazole: 400 mg orally twice daily

OR

Penicillin allergy with no previous clarithromycin exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily

--AND--

» clarithromycin: 500 mg orally (immediate-release) twice daily

--AND--

» metronidazole: 400 mg orally twice daily

OR

Penicillin allergy with previous clarithromycin exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily

Acute

--AND--

» bismuth subsalicylate: 525 mg orally four times daily

--AND--

» tetracycline: 500 mg orally four times daily

--AND--

» metronidazole: 400 mg orally twice daily

» Eradication regimens vary between guidelines and locations; traditional empirical 'triple therapies' rarely achieve satisfactory eradication rates and success rates vary according to local and regional resistance patterns.[86] Empirical therapies should be restricted to those shown to be highly effective locally.[87] Check local guidance and follow local protocols.

- Eradication therapy leads to ulcer healing and a dramatic decrease in ulcer recurrence.[84] Most regimens are 70% to 90% efficacious in practice, limited mainly by antibiotic resistance or patient adherence to the regimen.
- Check the patient's antibiotic history and allergy status, and stress the importance of adherence.
- To optimise the management of *H pylori* infection, base eradication therapy on patterns of local and individual antimicrobial resistance, if possible.[106] [107]
- Offer people with peptic ulcer (gastric or duodenal) and proven *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion.

» The regimens below are based on guidance from the UK's National Institute for Health and Care Excellence (NICE) and Public Health England but will often need to be substituted with local protocols that take account of resistance patterns because traditional empirical 'triple therapies' often fail to achieve successful eradication.[46] [48]

» For eradication therapy, prescribe triple therapy (a **proton-pump inhibitor [PPI] plus two antibiotics**) **first-line**.[46]

- A PPI plus amoxicillin plus either clarithromycin or metronidazole is the recommended first-line treatment option.[46] [48]

Acute

- In patients who are allergic to penicillin, first-line triple therapy consists of a PPI plus clarithromycin plus metronidazole.[46] [48]
- If patients who are allergic to penicillin have had previous clarithromycin exposure, give quadruple therapy with a PPI plus bismuth plus metronidazole plus tetracycline.[46] [48]
- Treatment course: 7 days.

» **Re-test patients** with peptic ulcer (gastric or duodenal) and who were initially *H pylori* positive, 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46]

- Leave a 2-week **washout** period after PPI use and a 4-week washout after antibiotic use before re-testing for *H pylori* with a breath test, as these drugs suppress bacteria and can lead to false negatives.[46] [48]

» In practice, in most patients, you will not need to continue long-term acid suppressive therapy after treatment of *H pylori* infection.

» All regimens contain antibiotics and therefore may cause diarrhoea, promote opportunistic infections, and interfere with absorption of many other drugs, including oral contraceptives. If diarrhoea develops, consider microscopic colitis (lymphocytic or collagenous colitis) and, more rarely, *Clostridium difficile* -associated disease. Review the need for treatment.[48]

consider **ulcer healing therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» esomeprazole: 20 mg orally once daily

OR

» lansoprazole: 30 mg orally once daily

OR

» omeprazole: 20 mg orally once daily

OR

» pantoprazole: 40 mg orally once daily

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OR

» rabeprazole: 20 mg orally once daily

Secondary options

» famotidine: 40 mg orally once daily at night

OR

» nizatidine: 300 mg orally once daily at night

» Consider offering ulcer healing therapy with a full-dose PPI or H2 antagonist for 8 weeks after eradication therapy is complete.

- This is standard practice in the UK based on clinical experience but bear in mind that ulcer healing therapy is not specifically recommended for this group by NICE.

» A specialist may advise eradication therapy before ulcer healing therapy or vice versa based on their clinical experience and preference.

» Always follow your local protocols and use your clinical judgement to determine optimal approach for your individual patient.

2nd **alternative H pylori eradication regimen**

Primary options

No penicillin allergy with no previous exposure to clarithromycin or metronidazole

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily

--AND--

» amoxicillin: 1000 mg orally twice daily

--AND--

» clarithromycin: 500 mg orally (immediate-release) twice daily
-or-
» metronidazole: 400 mg orally twice daily

OR

Acute

No penicillin allergy with previous exposure to clarithromycin and metronidazole

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» amoxicillin: 1000 mg orally twice daily
--AND--
» tetracycline: 500 mg orally four times daily
-or-
» levofloxacin: 250 mg orally twice daily

OR

Penicillin allergy with no previous fluoroquinolone exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» metronidazole: 400 mg orally twice daily
--AND--
» levofloxacin: 250 mg orally twice daily

OR

Penicillin allergy with previous fluoroquinolone exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» bismuth subsalicylate: 525 mg orally four times daily

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--AND--

» tetracycline: 500 mg orally four times daily

--AND--

» metronidazole: 400 mg orally twice daily

» If the first eradication treatment fails, try an alternative 7-day triple regimen.[46]

» Use a PPI plus amoxicillin plus either clarithromycin or metronidazole (**whichever was not used first-line**).[46] [48]

- If a patient has had previous exposure to clarithromycin and metronidazole offer a course of treatment with a PPI plus amoxicillin plus tetracycline (or, if a tetracycline cannot be used, levofloxacin).[46] [48]
- Offer people who are allergic to penicillin (and who have not had previous exposure to a fluoroquinolone antibiotic) a course of treatment with a PPI plus metronidazole plus levofloxacin.[46] [48]
- Offer people who are allergic to penicillin and who have had previous exposure to a fluoroquinolone antibiotic, a course of a PPI plus bismuth plus metronidazole plus tetracycline.[46]

Drug safety alert: Restrictions on the use of fluoroquinolone antibiotics

Fluoroquinolones are associated with serious, disabling, and potentially irreversible adverse effects including tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects. The European Medicines Agency recommends that fluoroquinolone antibiotics be restricted for use in serious, life-threatening bacterial infections only. Furthermore, they recommend that fluoroquinolones should not be used for mild to moderate infections unless other appropriate antibiotics for the specific infection cannot be used, and should not be used in non-severe, non-bacterial, or self-limiting infections. The UK-based Medicines and Healthcare products Regulatory Agency (MHRA) supports these recommendations.[108] [109]

» In areas with high rates of multiple drug resistance, pre-treatment antimicrobial susceptibility-guided therapy may be more effective than clarithromycin-based triple therapy

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alone for *H pylori* eradication.[107] However, *H pylori* culture and molecular testing is not widely available in all countries.[110]

3rd **referral to specialist service**

» Consider specialist referral for any patient in whom second-line *H pylori* eradication therapy has failed.[46]

with long-term use of non-steroidal anti-inflammatory drugs or low-dose aspirin

1st **ulcer healing therapy**

Primary options

» esomeprazole: 20 mg orally once daily

OR

» lansoprazole: 30 mg orally once daily

OR

» omeprazole: 20 mg orally once daily

OR

» pantoprazole: 40 mg orally once daily

OR

» rabeprazole: 20 mg orally once daily

Secondary options

» famotidine: 40 mg orally once daily at night

OR

» nizatidine: 300 mg orally once daily at night

» If the *H pylori* positive patient is a long-term user of NSAIDs (or low-dose aspirin):[46]

- Discontinue any NSAID the patient is taking, if possible.[46] If this is not possible, and in people at high risk (previous ulceration), consider a COX-2 inhibitor instead of a standard NSAID and prescribe a PPI.[46]
  - Weigh up the benefits versus risks of reducing or stopping any other potential ulcer-inducing drugs, including aspirin.[83] Seek senior/specialist advice if low-dose aspirin is being taken for secondary prevention of cardiovascular or cerebrovascular events as the

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benefits of continuing may need to take priority.[79]

- NICE recommends to:
  - Start ulcer healing therapy with a full-dose proton-pump inhibitor [PPI] or H2 antagonist for 8 weeks.[46]
  - Then offer *H pylori* eradication therapy (typically a 7-day course of triple therapy [PPI + two antibiotics]).[46] See *H pylori eradication therapy* below.

» In practice, a specialist may advise eradication therapy before ulcer healing therapy or vice-versa based on their clinical experience and preference. Always follow your local protocols and use your clinical judgment to determine the optimal approach for your individual patient.

plus **H pylori eradication therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

No penicillin allergy

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily

--AND--

» amoxicillin: 1000 mg orally twice daily

--AND--

» clarithromycin: 500 mg orally (immediate-release) twice daily
-or-
» metronidazole: 400 mg orally twice daily

OR

Penicillin allergy with no previous clarithromycin exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily

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-or-

» pantoprazole: 40 mg orally twice daily

-or-

» rabeprazole: 20 mg orally twice daily

--AND--

» clarithromycin: 500 mg orally (immediate-release) twice daily

--AND--

» metronidazole: 400 mg orally twice daily

OR

Penicillin allergy with previous clarithromycin exposure

» esomeprazole: 20 mg orally twice daily

-or-

» lansoprazole: 30 mg orally twice daily

-or-

» omeprazole: 20-40 mg orally twice daily

-or-

» pantoprazole: 40 mg orally twice daily

-or-

» rabeprazole: 20 mg orally twice daily

--AND--

» bismuth subsalicylate: 525 mg orally four times daily

--AND--

» tetracycline: 500 mg orally four times daily

--AND--

» metronidazole: 400 mg orally twice daily

» Eradication regimens vary between guidelines and locations; traditional empirical 'triple therapies' rarely achieve satisfactory eradication rates and success rates vary according to local and regional resistance patterns.[86] Empirical therapies should be restricted to those shown to be highly effective locally.[87] Check local guidance and follow local protocols.

- Eradication therapy leads to ulcer healing and a dramatic decrease in ulcer recurrence.[84] Most regimens are 70% to 90% efficacious in practice, limited mainly by antibiotic resistance or patient adherence to the regimen.
- Check the patient's antibiotic history and allergy status, and stress the importance of adherence.
- To optimise the management of *H pylori* infection, base eradication therapy on patterns of local and individual antimicrobial resistance, if possible.[106] [107]

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- Offer people with peptic ulcer (gastric or duodenal) and proven *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46]

» The regimens below are based on guidance from the UK's National Institute for Health and Care Excellence (NICE) and Public Health England but will often need to be substituted with local protocols that take account of resistance patterns because traditional empirical 'triple therapies' often fail to achieve successful eradication.[46] [48]

» Offer **7 days of *H pylori* eradication therapy** to people who have tested positive for *H pylori* and who have peptic ulcer disease.[46]

» For eradication therapy, prescribe triple therapy (a **proton-pump inhibitor [PPI] plus two antibiotics**) **first-line**.[46]

- A PPI plus amoxicillin plus either clarithromycin or metronidazole is the recommended first-line treatment option.[46] [48]
- In patients who are allergic to penicillin, first-line triple therapy consists of a PPI plus clarithromycin plus metronidazole.[46] [48]
- If patients who are allergic to penicillin have had previous clarithromycin exposure, give quadruple therapy with a PPI plus bismuth plus metronidazole plus tetracycline.[46] [48]
- Treatment course: 7 days.

» **Re-test patients** with peptic ulcer (gastric or duodenal) and who were initially *H pylori* positive, 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46]

- Leave a 2-week **washout** period after PPI use and a 4-week washout after antibiotic use before re-testing for *H pylori* with a breath test, as these drugs suppress bacteria and can lead to false negatives.[46] [48]

» In practice, in most patients, you will not need to continue long-term acid suppressive therapy after treatment of *H pylori* infection.

» All regimens contain antibiotics and therefore may cause diarrhoea, promote opportunistic infections, and interfere with absorption of many

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other drugs, including oral contraceptives. If diarrhoea develops, consider microscopic colitis (lymphocytic or collagenous colitis) and, more rarely, *Clostridium difficile* -associated disease. Review the need for treatment.[48]

2nd **alternative H pylori eradication regimen**

Primary options

No penicillin allergy with no previous exposure to clarithromycin or metronidazole

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» amoxicillin: 1000 mg orally twice daily
--AND--
» clarithromycin: 500 mg orally (immediate-release) twice daily
-or-
» metronidazole: 400 mg orally twice daily

OR

No penicillin allergy with previous exposure to clarithromycin and metronidazole

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» amoxicillin: 1000 mg orally twice daily
--AND--
» tetracycline: 500 mg orally four times daily
-or-
» levofloxacin: 250 mg orally twice daily

OR

Penicillin allergy with no previous fluoroquinolone exposure

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» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» metronidazole: 400 mg orally twice daily
--AND--
» levofloxacin: 250 mg orally twice daily

OR

Penicillin allergy with previous fluoroquinolone exposure

» esomeprazole: 20 mg orally twice daily
-or-
» lansoprazole: 30 mg orally twice daily
-or-
» omeprazole: 20-40 mg orally twice daily
-or-
» pantoprazole: 40 mg orally twice daily
-or-
» rabeprazole: 20 mg orally twice daily
--AND--
» bismuth subsalicylate: 525 mg orally four times daily
--AND--
» tetracycline: 500 mg orally four times daily
--AND--
» metronidazole: 400 mg orally twice daily

» If the first eradication treatment fails, try an alternative 7-day triple regimen.[46]

» Use a PPI plus amoxicillin plus either clarithromycin or metronidazole (**whichever was not used first-line**).[46] [48]

- If a patient has had previous exposure to clarithromycin and metronidazole offer a course of treatment with a PPI plus amoxicillin plus tetracycline (or, if a tetracycline cannot be used, levofloxacin).[46] [48]
- Offer people who are allergic to penicillin (and who have not had previous exposure to a fluoroquinolone antibiotic) a course of treatment with a PPI plus metronidazole plus levofloxacin.[46] [48]

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- Offer people who are allergic to penicillin and who have had previous exposure to a fluoroquinolone antibiotic, a course of a PPI plus bismuth plus metronidazole plus tetracycline.[46]

Drug safety alert: Restrictions on the use of fluoroquinolone antibiotics

Fluoroquinolones are associated with serious, disabling, and potentially irreversible adverse effects including tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects. The European Medicines Agency recommends that fluoroquinolone antibiotics be restricted for use in serious, life-threatening bacterial infections only. Furthermore, they recommend that fluoroquinolones should not be used for mild to moderate infections unless other appropriate antibiotics for the specific infection cannot be used, and should not be used in non-severe, non-bacterial, or self-limiting infections. The UK-based Medicines and Healthcare products Regulatory Agency (MHRA) supports these recommendations.[108] [109]

» In areas with high rates of multiple drug resistance, pre-treatment antimicrobial susceptibility-guided therapy may be more effective than clarithromycin-based triple therapy alone for *H pylori* eradication.[107] However, *H pylori* culture and molecular testing is not widely available in all countries.[110]

3rd **referral to specialist service**

» Consider specialist referral for any patient in whom second-line *H pylori* eradication therapy has failed.[46]

MANAGEMENT

Ongoing

recurrent or refractory ulcers

1st **long-term acid suppression therapy**

Primary options

» esomeprazole: 10 mg orally once daily

OR

» lansoprazole: 15 mg orally once daily

OR

» omeprazole: 10 mg orally once daily

OR

» pantoprazole: 20 mg orally once daily

OR

» rabeprazole: 10 mg orally once daily

Secondary options

» famotidine: 20 mg orally once daily at night

OR

» nizatidine: 150 mg orally once daily at night

» Long-term maintenance acid-suppression therapy may be used in selected high-risk patients (e.g., frequent recurrences, large or refractory ulcers) with or without *H pylori* infection. The preferred regimen and duration of therapy are uncertain, although most clinicians use a proton-pump inhibitor (PPI).

- If the organism cannot be eradicated despite repeated attempts, long-term acid suppression therapy may be necessary to control symptoms and prevent relapse.
- If symptoms continue or recur after initial treatment, prescribe a PPI or H2 antagonist at the lowest dose that controls symptoms.[46]
- Encourage patients to manage their own symptoms by using PPI treatment on an 'as-needed' basis.[46]

Ongoing

» Based on current data, the overall benefits of PPI treatment outweigh the potential risks in most patients.[97] However, various studies have suggested an association, though not necessarily a causal link, between long-term use of PPIs and increased risk of:[88] [91] [92] [93]

- Osteoporosis[89] [98]
- Pneumonia
- Dementia
- Stroke
- Type 2 diabetes[96]
- Enteric infection.[97]

Drug safety alert: Adverse events associated with long-term use of PPIs

Severe hypomagnesaemia has been reported infrequently in patients treated with PPIs, rarely after 3 months, but usually after 1 year of treatment. Serious features of hypomagnesaemia include fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia. Hypomagnesaemia usually improves after magnesium replacement and discontinuation of the PPI.[102]

PPIs have been associated with an increased risk of **osteoporosis** and a modest increase in the risk of hip, wrist, or spine fracture, especially if used by older people in high doses and for >1 year.[103]

PPIs have been linked rarely, but probably causally, to **subacute cutaneous lupus erythematosus** (SCLE).[104]

In being vigilant for these rare adverse events:

- Consider measuring magnesium levels before starting PPI treatment and periodically during prolonged treatment, especially in those who take concomitant digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics).[102]
- Treat patients at risk of osteoporosis according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.[103]
- Advise patients who develop arthralgia and skin lesions in sun-exposed areas to avoid sunlight, and consider giving topical or systemic corticosteroids if

Ongoing

there are no signs of remission after a few weeks or months.[104]

- Consider stopping the PPI unless it is imperative for a serious acid-related condition.
- Take into account any use of PPIs obtained over-the-counter.

» Offer H2 antagonist therapy if there is an inadequate response to a PPI.[46]

» In people with an unhealed ulcer, exclude non-adherence, malignancy, failure to detect *H pylori* , inadvertent or surreptitious NSAID use, other ulcer-inducing medication, and rare causes such as Zollinger–Ellison syndrome or Crohn's disease.[46]

» In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a cyclo-oxygenase-2 (COX-2) inhibitor instead of a standard NSAID. In either case, prescribe with a PPI.[46]

» Discuss the potential harm associated with NSAIDs with patients who continue to take them after a peptic ulcer has healed.[46]

- Review the need for NSAID use regularly (at least every 6 months)
- Offer a trial of NSAID use on a limited 'as needed' basis[46]
- Consider:[46]
  - Reducing the NSAID dose
  - Substituting the NSAID with paracetamol
  - Using an alternative analgesic
  - Using low-dose ibuprofen.

Emerging

LOAD Helicobacter pylori eradication regimen

A quadruple regimen consisting of levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOAD) has been studied; however, it has not been shown to be superior to current standard treatment.[111]

Rifabutin-based Helicobacter pylori eradication regimen

The US Food and Drug Administration has approved the first rifabutin-based eradication therapy for *H pylori* in adults. The regimen consists of omeprazole, rifabutin, and amoxicillin. In two phase III trials, rifabutin-based treatment demonstrated high efficacy in *H pylori* eradication compared with placebo and active comparator (amoxicillin with omeprazole).[112] [113] [114] [115]

Oral proton-pump inhibitor therapy for actively bleeding ulcers

Meta-analyses report comparable rates of recurrent bleeding among patients who were randomly assigned to oral or to intravenous proton-pump inhibitor (PPI) therapy for bleeding peptic ulcer.[116] [117] Oral PPI therapy may be considered in those patients with active bleeding from peptic ulcer disease who cannot receive an intravenous infusion or in settings without this resource.[118]

Potassium-competitive acid blockers

Potassium-competitive acid blockers, such as vonoprazan, are potent inhibitors of gastric acid secretion. The speed of onset of a significant reduction in acid secretion is more rapid than with PPIs. Vonoprazan-based dual and triple therapies for *H pylori* eradication are at least as effective as comparable PPI-based therapies. However, in western populations the overall rates of *H pylori* eradication from vonoprazan-based dual and triple therapies (65% to 84%) are generally below desirable rates (90%).[119] At present these treatment regimes cannot be recommended unless satisfactory results are shown in the relevant local population. The increased potency of potassium-competitive acid blockers may offer some theoretical benefits over PPI-based regimens for *H pylori* eradication but the overall efficacy and cost-effectiveness of such regimens remains to be determined. Vonoprazan is effective for the treatment and prevention of peptic ulcer disease and aspirin- and non-steroidal anti-inflammatory drug (NSAID)-induced peptic ulcers and may offer an alternative for PPI intolerance or toxicity.[120] [121] [122] [123]

Haemostatic forceps for acute peptic ulcer bleeding

Haemostatic forceps are an option for treating bleeding peptic ulcers.[59] [124] Results for haemostasis are comparable to thermal coagulation or using cap-mounted scope clips.[124] [125] However, training in this technique is not yet widespread and the equipment may be more expensive.

Primary prevention

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be used with caution, especially in people aged over 60 years and those who are taking corticosteroids, bisphosphonates, or other antithrombotic drugs.[24] [25] Concurrent use of a proton-pump inhibitor (PPI) has been shown to reduce the risk of gastrointestinal complications in patients taking long-term aspirin and/or oral anticoagulants.[36] [37] [38]

PPIs prevent peptic ulcers and complications in people who require NSAID therapy.[39] However, guidelines suggest considering a test and treat strategy for *Helicobacter pylori* before starting long-term NSAID therapy, as *H pylori* eradication has been shown to protect against aspirin-associated peptic ulcer bleeding.[40] [41]

Prophylactic use of a PPI is appropriate for patients in intensive care, especially those who require mechanical ventilation, those who are deemed at high risk of gastrointestinal bleeding due to comorbidities such as chronic liver disease, or those who have co-existing conditions such as coagulopathy, sepsis, or acute kidney injury.[33] [34] PPIs are generally accepted to be superior to H2 antagonists at preventing

clinically important gastrointestinal bleeding in critically ill patients.[34] [42] [43] Evidence from one double-blind randomised trial suggests that PPIs and H2 antagonists have similar efficacy in reducing the risk of upper gastrointestinal bleeding or ulcers in people taking low-dose aspirin.[44] A meta-analysis that evaluated H2 antagonists, PPIs, and prostaglandin analogues found that PPIs were more effective in preventing bleeding from ulcers than H2 antagonists and prostaglandin analogues.[45] PPIs were also more effective in healing ulcers and preventing recurrent bleeding and the need for blood transfusion.[45]

Secondary prevention

Discuss the potential harm associated with non-steroidal anti-inflammatory drugs (NSAIDs) with patients who continue to take them after a peptic ulcer has healed.[46]

- Review the need for NSAID use regularly (at least every 6 months).
- Offer a trial of NSAID use on a limited 'as needed' basis.[46]
- Consider:[46]
    - Reducing the NSAID dose
    - Substituting the NSAID with paracetamol
    - Using an alternative analgesic
    - Using low-dose ibuprofen.

In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a cyclo-oxygenase-2 (COX-2) inhibitor instead of a standard NSAID. In either case, prescribe with a proton-pump inhibitor (PPI).[46]

While avoidance of NSAIDs and cigarette smoking may decrease the risk of recurrence, the role of alcohol intake is less certain. Nonetheless avoidance of excessive alcohol intake is usually recommended.

Patient discussions

Patients should be advised to avoid non-steroidal anti-inflammatory drugs (NSAIDs); however, they should continue aspirin if indicated for secondary prevention of cardiovascular events.[59] They should discuss the risks and benefits of continuation of any other anticoagulants with their specialist.

If they have documented *H pylori* infection, they should be reminded that they need to complete the course of therapy even if symptoms resolve. Patients should seek medical attention if they develop blood in stools, black tarry stools, vomiting, or abdominal pain.

Advise people who need long-term management of dyspepsia symptoms that they should stop cigarette smoking, will need an annual review of their condition, and that they should try stepping down or stopping treatment (unless there is an underlying condition that needs continuing treatment).[46] [128] Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the counter and taken as needed).[46]

FOLLOW UP

Monitoring

Monitoring

People with gastric ulcer and *H pylori* should be followed up with a repeat endoscopy 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46] This enables the clinician to check ulcer healing and to rule out gastric cancer (because a small number of gastric cancers may present as gastric ulcers). Offer people with peptic ulcer (gastric or duodenal) and proven *H pylori* retesting for *H pylori* 6 to 8 weeks after beginning treatment, depending on the size of the lesion.[46] Patients with uncomplicated duodenal ulcers do not need follow-up endoscopy.

Ideally, the patient should stop proton-pump inhibitor (PPI) therapy for at least 14 days and antibiotics 28 days prior to eradication testing as these drugs suppress bacteria and can lead to false negatives.[46] [48]

Complications

Complications	Timeframe	Likelihood
penetration	**long term**	**low**
Occurs when chronic ulcer penetrates the entire thickness of the stomach or duodenal wall, into an adjacent organ such as the pancreas, but without free perforation into the peritoneal cavity. Management is the same as that for standard ulcer therapy; however, surgery is sometimes necessary.		
gastric outlet obstruction	**long term**	**low**
Gastric outlet obstruction from chronic pyloric stenosis may occur as pyloric channel ulcers heal with scarring and oedema. May present with nausea, vomiting, and weight loss. A succussion splash may be elicited on examination. Management is aimed at treating the cause of the ulcer. High-dose proton-pump inhibitors are also used in the management of this condition. Endoscopic dilation is often helpful, with surgery reserved for refractory patients.		
upper gastrointestinal (GI) bleeding	**variable**	**medium**
Peptic ulcer disease is the cause of around 35% of cases of life-threatening acute upper gastrointestinal bleeding.[56] [127] Bleeding is an infrequent complication of peptic ulcers but the most common cause of hospitalisation and mortality. It occurs when an ulcer erodes into the wall of a gastroduodenal blood vessel. Despite the decrease in *Helicobacter pylori* incidence, peptic ulcer disease remains a major issue, largely due to the use of non-steroidal anti-inflammatory drugs (NSAIDs) in older patients. NSAIDs are the major risk factor for peptic ulcer bleeding and promote bleeding partly through their anti-platelet effects.[12] Patients with overt bleeding (haematemesis and/or melaena and/or shock) should be evaluated in the emergency department and endoscopy should be performed promptly.		
perforation	**variable**	**low**
Caused by erosion of the ulcer through the wall of the stomach or duodenum into the peritoneal cavity. Most perforations occur in older patients, in patients taking NSAIDs and in patients with ulcers in the duodenum or gastric antrum. Usual presentation is with shock and peritonitis. Patients should be referred to the emergency department for surgical evaluation.		

FOLLOW UP

Prognosis

With proton-pump inhibitor (PPI) therapy, duodenal ulcers typically heal within 4 weeks and gastric ulcers within 8 weeks.[126]

For patients with peptic ulcers caused by *Helicobacter pylori*, the prognosis post *H pylori* eradication is good: the rate of recurrence of a duodenal ulcer is reduced from approximately 64% without treatment to approximately 14% with eradication therapy, and the rate of recurrence of a gastric ulcer is reduced from approximately 52% without treatment to approximately 15% with eradication therapy.[84] *H pylori* eradication is also beneficial in those with complicated ulcer disease.

For ulcers associated with use of non-steroidal anti-inflammatory drugs (NSAIDs), discontinuing the NSAID (and eradicating *H pylori* if present) will lead to a low rate of ulcer recurrence. In patients who continue using NSAIDs, ulcer recurrence is high, and thus coprescription of a PPI is advisable.

Diagnostic guidelines

United Kingdom

Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Helicobacter pylori in dyspepsia: test and treat

Published by: Public Health England **Last published:** 2019

International

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants

Published by: British Society of Gastroenterology; European Society of Gastrointestinal Endoscopy **Last published:** 2021

North America

CDC health information for international travel (the yellow book): Helicobacter pylori

Published by: US Centers for Disease Control and Prevention **Last published:** 2023

ACR appropriateness criteria: epigastric pain

Published by: American College of Radiology **Last published:** 2021

ACG and CAG clinical guideline: management of dyspepsia

Published by: American Society for Gastrointestinal Endoscopy; Canadian Association of Gastroenterology **Last published:** 2017

The role of endoscopy in the management of patients with peptic ulcer disease

Published by: American Society for Gastrointestinal Endoscopy **Last published:** 2010 (reviewed in 2015)

Treatment guidelines

United Kingdom

Haematological management of major haemorrhage

Published by: British Society for Haematology **Last published:** 2022

British Society of Gastroenterology (BSG)-led multisociety consensus care bundle for the early clinical management of acute upper gastrointestinal bleeding

Published by: British Society of Gastroenterology **Last published:** 2020

Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Helicobacter pylori in dyspepsia: test and treat

Published by: Public Health England **Last published:** 2019

Acute upper gastrointestinal bleeding in over 16s: management

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Europe

Current concepts in the management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report

Published by: European Helicobacter Study Group **Last published:** 2022

Spanish consensus conference on Helicobacter pylori infection treatment

Published by: Spanish Consensus Conference **Last published:** 2022

Management of Helicobacter pylori infection

Published by: Italian Society of Gastroenterology; Italian Society of Digestive Endoscopy **Last published:** 2022

Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH)

Published by: European Society of Gastrointestinal Endoscopy **Last published:** 2021

International

Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants

Published by: British Society of Gastroenterology; European Society of Gastrointestinal Endoscopy **Last published:** 2021

World Gastroenterology Organisation global guidelines: Helicobacter pylori

Published by: World Gastroenterology Organisation **Last published:** 2021

Perforated and bleeding peptic ulcer

Published by: World Society of Emergency Surgery **Last published:** 2020

North America

ACG clinical guideline: treatment of Helicobacter pylori infection

Published by: American College of Gastroenterology **Last published:** 2024

CDC health information for international travel (the yellow book): Helicobacter pylori

Published by: US Centers for Disease Control and Prevention **Last published:** 2023

American College of Gastroenterology-Canadian Association of Gastroenterology clinical practice guideline: management of anticoagulants and antiplatelets during acute gastrointestinal bleeding and the periendoscopic period

Published by: American Society for Gastrointestinal Endoscopy; Canadian Association of Gastroenterology **Last published:** 2022

ACG clinical guideline: upper gastrointestinal and ulcer bleeding

Published by: American College of Gastroenterology **Last published:** 2021

ACG and CAG clinical guideline: management of dyspepsia

Published by: American Society for Gastrointestinal Endoscopy; Canadian Association of Gastroenterology **Last published:** 2017

Asia

Evidence-based clinical practice guidelines for peptic ulcer disease

Published by: Japanese Society of Gastroenterology **Last published:** 2020

Guidelines for the management of Helicobacter pylori infection in Japan

Published by: Japanese Society for Helicobacter Research **Last published:** 2019

Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding

Published by: Asia-Pacific working group **Last published:** 2018

Oceania

Management of dyspepsia and heartburn

Published by: New Zealand Guidelines Group **Last published:** 2004

Evidence tables

In people with upper gastrointestinal bleeding, what are the effects of tranexamic acid?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer

Evidence B *

Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes.

Population: People (where reported, mean age 56-63 years; 73% men) with suspected or endoscopically verified upper gastrointestinal bleeding

Intervention: Tranexamic acid #

Comparison: Placebo #

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Mortality at 2-3 weeks #	Favours intervention	Moderate
Rebleeding or continued bleeding at 2-3 weeks	No statistically significant difference	Low
Surgery at 2-3 weeks	No statistically significant difference	Moderate
Transfusion required at 2-3 weeks (post hoc analysis)	No statistically significant difference	Very Low
Adverse events: composite of myocardial infarction, pulmonary embolism, and cerebral infarction	No statistically significant difference	GRADE assessment not performed for this outcome
Adverse events: deep venous thrombosis	No statistically significant difference	GRADE assessment not performed for this outcome
Adverse events: any thromboembolic event	No statistically significant difference	GRADE assessment not performed for this outcome

Note

EVIDENCE TABLES

This evidence table summarises the findings for the comparison of tranexamic acid versus placebo, which is the main comparison as stated in the Cochrane review Summary of Findings table. See the full Cochrane Clinical Answer (CCA) for information on other comparisons (tranexamic acid versus cimetidine or lansoprazole).

The reviewers carried out a sensitivity analysis where in a worst-case scenario analysis for this outcome (patients with missing outcome data were included as treatment failures) there was no statistically significant difference between groups (GRADE assessment not performed).

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE?

Key articles

- National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Oct 2019 [internet publication]. Full text
- UK Health Security Agency. Helicobacter pylori in dyspepsia: test and treat. Jan 2025 [internet publication]. Full text
- Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017 Jul;112(7):988-1013. Full text Abstract
- National Institute for Health and Care Excellence. Acute upper gastrointestinal bleeding in over 16s: management. August 2016 [internet publication]. Full text
- Siau K, Hearnshaw S, Stanley AJ, et al. British Society of Gastroenterology (BSG)-led multisociety consensus care bundle for the early clinical management of acute upper gastrointestinal bleeding. Frontline Gastroenterol. 2020;11(4):311-23. Full text Abstract

References

1. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther. 2009 May 1;29(9):938-46. Full text Abstract
2. Li Z, Zou D, Ma X, et al. Epidemiology of peptic ulcer disease: endoscopic results of the systematic investigation of gastrointestinal disease in China. Am J Gastroenterol. 2010 Aug 24;105(12):2570-7. Abstract
3. Aro P, Storskrubb T, Ronkainen J, et al. Peptic ulcer disease in a general adult population: the Kalixanda study: a random population-based study. Am J Epidemiol. 2006 Jun 1;163(11):1025-34. Abstract
4. Sonnenberg A. Temporal trends and geographical variations of peptic ulcer disease. Aliment Pharmacol Ther. 1995;9 Suppl 2:3-12. Abstract
5. Sonnenberg A. Time trends of ulcer mortality in Europe. Gastroenterology. 2007 Jun;132(7):2320-7. Full text Abstract
6. Cai S, García Rodríguez LA, Massó-González EL, et al. Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. Aliment Pharmacol Ther. 2009 Nov 15;30(10):1039-48. Full text Abstract
7. Nam K, Shin JE, Kim SE, et al. Prevalence and risk factors for upper gastrointestinal diseases in health check-up subjects: a nationwide multicenter study in Korea. Scand J Gastroenterol. 2018 Aug;53(8):910-6. Abstract

REFERENCES

8. Ren J, Jin X, Li J, et al. The global burden of peptic ulcer disease in 204 countries and territories from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. Int J Epidemiol. 2022 Oct 13;51(5):1666-76. Abstract

9. Azhari H, King JA, Coward S, et al. The global incidence of peptic ulcer disease is decreasing since the turn of the 21st century: a study of the Organisation for Economic Co-Operation and Development (OECD). Am J Gastroenterol. 2022 Sep 1;117(9):1419-27. Abstract

10. Suerbaum S, Michetti P. Helicobacter pylori infection. New Engl J Med. 2002 Oct 10;347(15):1175-86. Abstract

11. Archampong TN, Asmah RH, Richards CJ, et al. Gastro-duodenal disease in Africa: literature review and clinical data from Accra, Ghana. World J Gastroenterol. 2019 Jul 14;25(26):3344-58. Full text Abstract

12. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet. 2002 Jan 5;359(9300):14-22. Abstract

13. Hung LC, Ching JY, Sung JJ, et al. Long-term outcome of Helicobacter pylori-negative idiopathic bleeding ulcers: a prospective cohort study. Gastroenterology. 2005 Jun;128(7):1845-50. Abstract

14. Dore MP, Soro S, Niolu C, et al. Clinical features and natural history of idiopathic peptic ulcers: a retrospective case-control study. Scand J Gastroenterol. 2019 Nov;54(11):1315-21. Abstract

15. Levenstein S, Rosenstock S, Jacobsen RK, et al. Psychological stress increases risk for peptic ulcer, regardless of Helicobacter pylori infection or use of nonsteroidal anti-inflammatory drugs. Clin Gastroenterol Hepatol. 2015 Mar;13(3):498-506. Full text Abstract

16. Kanno T, Iijima K, Abe Y, et al. Peptic ulcers after the Great East Japan earthquake and tsunami: possible existence of psychosocial stress ulcers in humans. J Gastroenterol. 2013 Apr;48(4):483-90. Abstract

17. Cekin AH, Taskoparan M, Duman A, et al. The role of Helicobacter pylori and NSAIDs in the pathogenesis of uncomplicated duodenal ulcer. Gastroenterol Res Pract. 2012;2012:189373. Full text Abstract

18. Narayanan M, Reddy KM, Marsicano E. Peptic Ulcer Disease and Helicobacter pylori infection. Mo Med. 2018 May-Jun;115(3):219-24. Full text Abstract

19. O'Connor HJ. The role of Helicobacter pylori in peptic ulcer disease. Scand J Gastroenterol Suppl. 1994;201:11-5. Abstract

20. Lazzaroni M, Bianchi Porro G. Gastrointestinal side-effects of traditional nonsteroidal anti-inflammatory drugs and new formulations. Aliment Pharmacol Ther. 2004 Jul;20(suppl 2):48-58. Abstract

21. Mahady SE, Margolis KL, Chan A, et al. Major GI bleeding in older persons using aspirin: incidence and risk factors in the ASPREE randomised controlled trial. Gut. 2021 Apr;70(4):717-24. Full text Abstract

22. Russell RI. Non-steroidal anti-inflammatory drugs and gastrointestinal damage-problems and solutions. Postgrad Med J. 2001 Feb;77(904):82-8. Full text Abstract

23. Drini M. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. Aust Prescr. 2017 Jun;40(3):91-3. Full text Abstract

24. García Rodríguez LA, Lin KJ, Hernández-Díaz S, et al. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. Circulation. 2011 Mar 15;123(10):1108-15. Full text Abstract

25. Knopp-Sihota JA, Cummings GG, Homik J, et al. The association between serious upper gastrointestinal bleeding and incident bisphosphonate use: a population-based nested cohort study. BMC Geriatr. 2013 Apr 20;13:36. Full text Abstract

26. Hooper L, Brown TJ, Elliott R, et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by nonsteroidal anti-inflammatory drugs: systematic review. BMJ. 2004 Oct 23;329(7472):948. Abstract

27. Tang CL, Ye F, Liu W, Pan XL, et al. Eradication of Helicobacter pylori infection reduces the incidence of peptic ulcer disease in patients using nonsteroidal anti-inflammatory drugs: a meta-analysis. Helicobacter. 2012 Aug;17(4):286-96. Abstract

28. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. Dig Dis Sci. 2009 Jan 22;55(1):66-72. Abstract

29. Maity P, Biswas K, Roy S, et al. Smoking and the pathogenesis of gastroduodenal ulcer--recent mechanistic update. Mol Cell Biochem. 2003 Nov;253(1-2):329-38. Abstract

30. Brenner H, Rothenbacher D, Bode G, et al. The individual and joint contributions of Helicobacter pylori infection and family history to the risk for peptic ulcer disease. J Infect Dis. 1998 Apr;177(4):1124-7. Abstract

31. Johnsen R, Førde OH, Straume B, et al. Aetiology of peptic ulcer: a prospective population study in Norway. J Epidemiol Community Health. 1994 Apr;48(2):156-60. Abstract

32. Del Bianco T, Borgoni R, Del Bianco P, et al. Peptic ulcer inheritance in patients with elevated serum pepsinogen group A levels and without infection of Helicobacter pylori. Dig Liver Dis. 2000 Jan-Feb;32(1):12-9. Abstract

33. Cash BD. Evidence-based medicine as it applies to acid suppression in the hospitalized patient. Crit Care Med. 2002 Jun;30(suppl 6):S373-8. Abstract

34. Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. BMJ. 2020 Jan 6;368:l6722. Full text Abstract

35. Chang WP, Peng YX. Differences between fixed day shift workers and rotating shift workers in gastrointestinal problems: a systematic review and meta-analysis. Ind Health. 2021 Mar 24;59(2):66-77. Full text Abstract

REFERENCES

36. Scheiman JM, Devereaux PJ, Herlitz J, et al. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). Heart. 2011 May;97(10):797-802. Full text Abstract

37. Kurlander JE, Barnes GD, Fisher A, et al. Association of Antisecretory Drugs with Upper Gastrointestinal Bleeding in Patients Using Oral Anticoagulants: A Systematic Review and Meta-Analysis. Am J Med. 2022 Oct;135(10):1231-1243.e8. Full text Abstract

38. Ahn HJ, Lee SR, Choi EK, et al. Protective effect of proton-pump inhibitor against gastrointestinal bleeding in patients receiving oral anticoagulants: a systematic review and meta-analysis. Br J Clin Pharmacol. 2022 Nov;88(11):4676-87. Abstract

39. Yang M, He M, Zhao M, et al. Proton pump inhibitors for preventing non-steroidal anti-inflammatory drug induced gastrointestinal toxicity: a systematic review. Curr Med Res Opin. 2017 Jan 25;33(6):973-80. Abstract

40. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38. Abstract

41. Hawkey C, Avery A, Coupland CAC, et al. Helicobacter pylori eradication for primary prevention of peptic ulcer bleeding in older patients prescribed aspirin in primary care (HEAT): a randomised, double-blind, placebo-controlled trial. Lancet. 2022 Nov 5;400(10363):1597-606. Full text Abstract

42. Alshamsi F, Belley-Cote E, Cook D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care. 2016 May 4;20(1):120. Full text Abstract

43. Alhazzani W, Alshamsi F, Belley-Cote E, et al. Efficacy and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. Intensive Care Med. 2017 Dec 4;44(1):1-11. Full text Abstract

44. Chan FK, Kyaw M, Tanigawa T, et al. Similar efficacy of proton-pump inhibitors vs H2-receptor antagonists in reducing risk of upper gastrointestinal bleeding or ulcers in high-risk users of low-dose aspirin. Gastroenterology. 2016 Sep 15;152(1):105-10.e1. Abstract

45. Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol. 2018 Apr;3(4):231-41. Full text Abstract

46. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Oct 2019 [internet publication]. Full text

47. National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. Apr 2025 [internet publication]. Full text

48. UK Health Security Agency. Helicobacter pylori in dyspepsia: test and treat. Jan 2025 [internet publication]. Full text

49. Moayyedi PM, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017 Jul;112(7):988-1013. Full text Abstract

50. Veitch AM, Radaelli F, Alikhan R, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. Endoscopy. 2021 Sep;53(9):947-69. Full text Abstract

51. Makristathis A, Hirschl AM, Mégraud F, et al. Review: diagnosis of Helicobacter pylori infection. Helicobacter. 2019 Sep;24 Suppl 1:e12641. Abstract

52. Malfertheiner P, Camargo MC, El-Omar E, et al. Helicobacter pylori infection. Nat Rev Dis Primers. 2023 Apr 20;9(1):19. Full text Abstract

53. Malfertheiner P, Megraud F, Rokkas T, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut. 2022 Aug 8 [Epub ahead of print]. Full text Abstract

54. Best LM, Takwoingi Y, Siddique S, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018;(3):CD012080. Full text Abstract

55. McNulty C, Teare L, Owen R, et al. Test and treat for dyspepsia--but which test? BMJ. 2005 Jan 15;330(7483):105-6. Full text Abstract

56. National Institute for Health and Care Excellence. Acute upper gastrointestinal bleeding in over 16s: management. August 2016 [internet publication]. Full text

57. Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ. 2017 Jan 4;356:i6432. Full text Abstract

58. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet. 2000 Oct 14;356(9238):1318-21. Abstract

59. Gralnek IM, Stanley AJ, Morris AJ, et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) guideline - update 2021. Endoscopy. 2021 Mar;53(3):300-32. Full text Abstract

60. Stanworth SJ, Dowling K, Curry N, et al. Haematological management of major haemorrhage: a British Society for Haematology guideline. Br J Haematol. 2022 Aug;198(4):654-67. Full text Abstract

61. Laine L, Barkun AN, Saltzman JR, et al. ACG clinical guideline: upper gastrointestinal and ulcer bleeding. Am J Gastroenterol. 2021 May 1;116(5):899-917. Full text Abstract

62. Choi IJ, Kim CG, Lee JY, et al. Family history of gastric cancer and Helicobacter pylori treatment. N Engl J Med. 2020 Jan 30;382(5):427-36. Full text Abstract

63. Chey WD, Howden CW, Moss SF, et al. ACG clinical guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2024 Sep 1;119(9):1730-53. Full text Abstract

64. Siau K, Hearnshaw S, Stanley AJ, et al. British Society of Gastroenterology (BSG)-led multisociety consensus care bundle for the early clinical management of acute upper gastrointestinal bleeding. Frontline Gastroenterol. 2020;11(4):311-23. Full text Abstract

65. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut. 1996 Mar;38(3):316-21. Full text Abstract

66. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jun 20;395(10241):1927-36. Full text Abstract

67. Roberts I, Shakur-Still H, Afolabi A, et al. A high-dose 24-hour tranexamic acid infusion for the treatment of significant gastrointestinal bleeding: HALT-IT RCT. Health Technol Assess. 2021 Oct;25(58):1-86. Full text Abstract

68. Dionne JC, Oczkowski SJW, Hunt BJ, et al. Tranexamic acid in gastrointestinal bleeding: a systematic review and meta-analysis. Crit Care Med. 2022 Mar 1;50(3):e313-9. Abstract

69. Lau JYW, Yu Y, Tang RSY, et al. Timing of endoscopy for acute upper gastrointestinal bleeding. N Engl J Med. 2020 Apr 2;382(14):1299-308. Full text Abstract

70. Lau JYW. Management of acute upper gastrointestinal bleeding: Urgent versus early endoscopy. Dig Endosc. 2022 Jan;34(2):260-4. Full text Abstract

71. Guo CLT, Wong SH, Lau LHS, et al. Timing of endoscopy for acute upper gastrointestinal bleeding: a territory-wide cohort study. Gut. 2022 Aug;71(8):1544-50. Full text Abstract

72. Marmo R, Rotondano G, Piscopo R, et al. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. Am J Gastroenterol. 2007 Feb;102(2):279-89; quiz 469. Abstract

73. Jensen DM, Kovacs T, Ghassemi KA, et al. Randomized controlled trial of over-the-scope clip as initial treatment of severe nonvariceal upper gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2021 Nov;19(11):2315-23. Full text Abstract

74. Schmidt A, Gölder S, Goetz M, et al. Over-the-scope clips are more effective than standard endoscopic therapy for patients with recurrent bleeding of peptic ulcers. Gastroenterology. 2018 Sep;155(3):674-86. Full text Abstract

75. Mullady DK, Wang AY, Waschke KA. AGA clinical practice update on endoscopic therapies for non-variceal upper gastrointestinal bleeding: expert review. Gastroenterology. 2020 Sep;159(3):1120-8. Full text Abstract

76. Hussein M, Alzoubaidi D, Lopez MF, et al. Hemostatic spray powder TC-325 in the primary endoscopic treatment of peptic ulcer-related bleeding: multicenter international registry. Endoscopy. 2021 Jan;53(1):36-43. Abstract

77. Kanno T, Yuan Y, Tse F, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2022 Jan 7;1(1):CD005415. Full text Abstract

78. Tarasconi A, Coccolini F, Biffl WL, et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg. 2020 Jan 7;15:3. Full text Abstract

79. Abraham NS, Barkun AN, Sauer BG, et al. American College of Gastroenterology-Canadian Association of Gastroenterology clinical practice guideline: management of anticoagulants and antiplatelets during acute gastrointestinal bleeding and the periendoscopic period. Am J Gastroenterol. 2022 Apr 1;117(4):542-58. Full text Abstract

80. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006 Nov;27(22):2667-74. Full text Abstract

81. Maulaz AB, Bezerra DC, Michel P, et al. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol. 2005 Aug;62(8):1217-20. Full text Abstract

82. Musumba C, Jorgensen A, Sutton L, et al. The relative contribution of NSAIDs and Helicobacter pylori to the aetiology of endoscopically-diagnosed peptic ulcer disease: observations from a tertiary referral hospital in the UK between 2005 and 2010. Aliment Pharmacol Ther. 2012 Jul;36(1):48-56. Abstract

83. National Institute for Health and Care Excellence. Clinical knowledge summaries: proven peptic ulcer - management. October 2019 [internet publication]. Full text

84. Ford AC, Gurusamy KS, Delaney B, et al. Eradication therapy for peptic ulcer disease in Helicobacter pylori-positive people. Cochrane Database Syst Rev. 2016;(4):CD003840. Full text Abstract

85. Guo CG, Cheung KS, Zhang F, et al. Delay in retreatment of Helicobacter pylori infection increases risk of upper gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2021 Feb;19(2):314-22. Full text Abstract

86. Graham DY. Implications of the paradigm shift in management of Helicobacter pylori infections. Therap Adv Gastroenterol. 2023 Mar 18;16:17562848231160858. Full text Abstract

87. Shiotani A, Roy P, Lu H, et al. Helicobacter pylori diagnosis and therapy in the era of antimicrobial stewardship. Therap Adv Gastroenterol. 2021 Dec 21;14:17562848211064080. Full text Abstract

88. Xie Y, Bowe B, Yan Y, et al. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ. 2019 May 29;365:l1580. Full text Abstract

89. Poly TN, Islam MM, Yang HC, et al. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. Osteoporos Int. 2019 Jan;30(1):103-14. Abstract

90. Chrysant SG. Proton pump inhibitor-induced hypomagnesemia complicated with serious cardiac arrhythmias. Expert Rev Cardiovasc Ther. 2019 May;17(5):345-51. Abstract

REFERENCES

91. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci. 2011 Apr;56(4):931-50. Abstract

92. Heidelbaugh JJ, Kim AH, Chang R, et al. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol. 2012 Jul;5(4):219-32. Full text Abstract

93. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol. 2013 Jul;6(4):443-51. Abstract

94. Brown JP, Tazare JR, Williamson E, et al. Proton pump inhibitors and risk of all-cause and cause-specific mortality: a cohort study. Br J Clin Pharmacol. 2021 Aug;87(8):3150-61. Full text Abstract

95. Veettil SK, Sadoyu S, Bald EM, et al. Association of proton-pump inhibitor use with adverse health outcomes: a systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials. Br J Clin Pharmacol. 2022 Feb;88(4):1551-66. Full text Abstract

96. Yuan J, He Q, Nguyen LH, et al. Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies. Gut. 2020 Sep 28 [online ahead of print]. Abstract

97. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019 Sep;157(3):682-691.e2. Full text Abstract

98. Hansen KE, Nieves JW, Nudurupati S, et al. Dexlansoprazole and esomeprazole do not affect bone homeostasis in healthy postmenopausal women. Gastroenterology. 2019 Mar;156(4):926-934.e6. Full text Abstract

99. Khan MA, Yuan Y, Iqbal U, et al. No association linking short-term proton pump inhibitor use to dementia: systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2020 May;115(5):671-8. Abstract

100. Ahn N, Nolde M, Krause E, et al. Do proton pump inhibitors increase the risk of dementia? A systematic review, meta-analysis and bias analysis. Br J Clin Pharmacol. 2023 Feb;89(2):602-16. Full text Abstract

101. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. Gut. 2016 May;65(5):740-8. Full text Abstract

102. Medicines and Healthcare products Regulatory Agency. Proton pump inhibitors in long-term use: reports of hypomagnesaemia. December 2014 [internet publication]. Full text

103. Medicines and Healthcare products Regulatory Agency. Proton pump inhibitors in long-term use: increased risk of fracture. December 2014 [internet publication]. Full text

104. Medicines and Healthcare products Regulatory Agency. Proton pump inhibitors: very low risk of subacute cutaneous lupus erythematosus. September 2015 [internet publication]. Full text

105. Richardson C, Hawkey CJ, Stack WA. Proton pump inhibitors - pharmacology and rationale for use in gastrointestinal disorders. Drugs. 1998 Sep;56(3):307-35. Abstract

106. Flores-Treviño S, Mendoza-Olazarán S, Bocanegra-Ibarias P, et al. Helicobacter pylori drug resistance: therapy changes and challenges. Expert Rev Gastroenterol Hepatol. 2018 Aug;12(8):819-27. Abstract

107. Fallone CA, Moss SF, Malfertheiner P. Reconciliation of recent Helicobacter pylori treatment guidelines in a time of increasing resistance to antibiotics. Gastroenterology. 2019 Jul;157(1):44-53. Full text Abstract

108. European Medicines Agency. Quinolone- and fluoroquinolone-containing medicinal products. March 2019 [internet publication]. Full text

109. Medicines and Healthcare products Regulatory Agency. Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects. March 2019 [internet publication]. Full text

110. Park CS, Lee SM, Park CH, et al. Pretreatment antimicrobial susceptibility-guided vs. clarithromycin-based triple therapy for Helicobacter pylori eradication in a region with high rates of multiple drug resistance. Am J Gastroenterol. 2014 Oct;109(10):1595-602. Abstract

111. Liou JM, Jiang XT, Chen CC, et al. Second-line levofloxacin-based quadruple therapy versus bismuth-based quadruple therapy for Helicobacter pylori eradication and long-term changes to the gut microbiota and antibiotic resistome: a multicentre, open-label, randomised controlled trial. Lancet Gastroenterol Hepatol. 2023 Mar;8(3):228-41. Full text Abstract

112. ClinicalTrials.gov. ERADICATE Hp: treating Helicobacter pylori with RHB-105 (ERADICATE Hp). September 2019 [internet publication]. Full text

113. ClinicalTrials.gov. ERADICATE Hp2: treating Helicobacter pylori with RHB-105 compared to active comparator (ERADICATE Hp2). March 2020 [internet publication]. Full text

114. Graham DY, Canaan Y, Maher J, et al. Rifabutin-based triple therapy (RHB-105) for Helicobacter pylori eradication: a double-blind, randomized, controlled trial. Ann Intern Med. 2020 Jun 16;172(12):795-802. Abstract

115. Xirouchakis E, Georgopoulos SD. Evaluating treatments with rifabutin and amoxicillin for eradication of Helicobacter pylori infection in adults: a systematic review. Expert Opin Pharmacother. 2022 Feb;23(2):201-10. Abstract

116. Jian Z, Li H, Race NS, et al. Is the era of intravenous proton pump inhibitors coming to an end in patients with bleeding peptic ulcers? Meta-analysis of the published literature. Br J Clin Pharmacol. 2016 Jun 12;82(3):880-9. Full text Abstract

117. Tringali A, Manta R, Sica M, et al. Comparing intravenous and oral proton pump inhibitor therapy for bleeding peptic ulcers following endoscopic management: a systematic review and meta-analysis. Br J Clin Pharmacol. 2017 Aug;83(8):1619-35. Full text Abstract

118. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. JAMA Intern Med. 2014 Nov;174(11):1755-62. Full text Abstract

REFERENCES

119. Chey WD, Mégraud F, Laine L, et al. Vonoprazan triple and dual therapy for Helicobacter pylori infection in the United States and Europe: randomized clinical trial. Gastroenterology. 2022 Sep;163(3):608-19. Full text Abstract

120. Marabotto E, Ziola S, Savarino V, et al. Vonoprazan fumarate for the treatment of gastric ulcers: a short review on emerging data. Clin Exp Gastroenterol. 2020 Apr 15;13:99-104. Full text Abstract

121. Kawai T, Oda K, Funao N, et al. Vonoprazan prevents low-dose aspirin-associated ulcer recurrence: randomised phase 3 study. Gut. 2018 Jun;67(6):1033-41. Full text Abstract

122. Mizokami Y, Oda K, Funao N, et al. Vonoprazan prevents ulcer recurrence during long-term NSAID therapy: randomised, lansoprazole-controlled non-inferiority and single-blind extension study. Gut. 2018 Jun;67(6):1042-51. Full text Abstract

123. Moraes-Filho JPP, Domingues G, Chinzon D, et al. Vonoprazan in the management of gastric/peptic ulcers: a systematic review of safety data. Prz Gastroenterol. 2022;17(4):266-73. Full text Abstract

124. Kim JW, Jang JY, Lee CK, et al. Comparison of hemostatic forceps with soft coagulation versus argon plasma coagulation for bleeding peptic ulcer--a randomized trial. Endoscopy. 2015 Aug;47(8):680-7. Abstract

125. Toka B, Eminler AT, Karacaer C, et al. Comparison of monopolar hemostatic forceps with soft coagulation versus hemoclip for peptic ulcer bleeding: a randomized trial (with video). Gastrointest Endosc. 2019 Apr;89(4):792-802. Abstract

126. Dexcel Pharma Ltd. Summary of product characteristics: omeprazole 20 mg gastro-resistant tablets. March 2023 [internet publication]. Full text

127. Boonpongmanee S, Fleischer DE, Pezzullo JC, et al. The frequency of peptic ulcer as a cause of upper-GI bleeding is exaggerated. Gastrointest Endosc. 2004 Jun;59(7):788-94. Abstract

128. Targownik LE, Fisher DA, Saini SD. AGA clinical practice update on de-prescribing of proton pump inhibitors: expert review. Gastroenterology. 2022 Apr;162(4):1334-42. Full text Abstract

Images

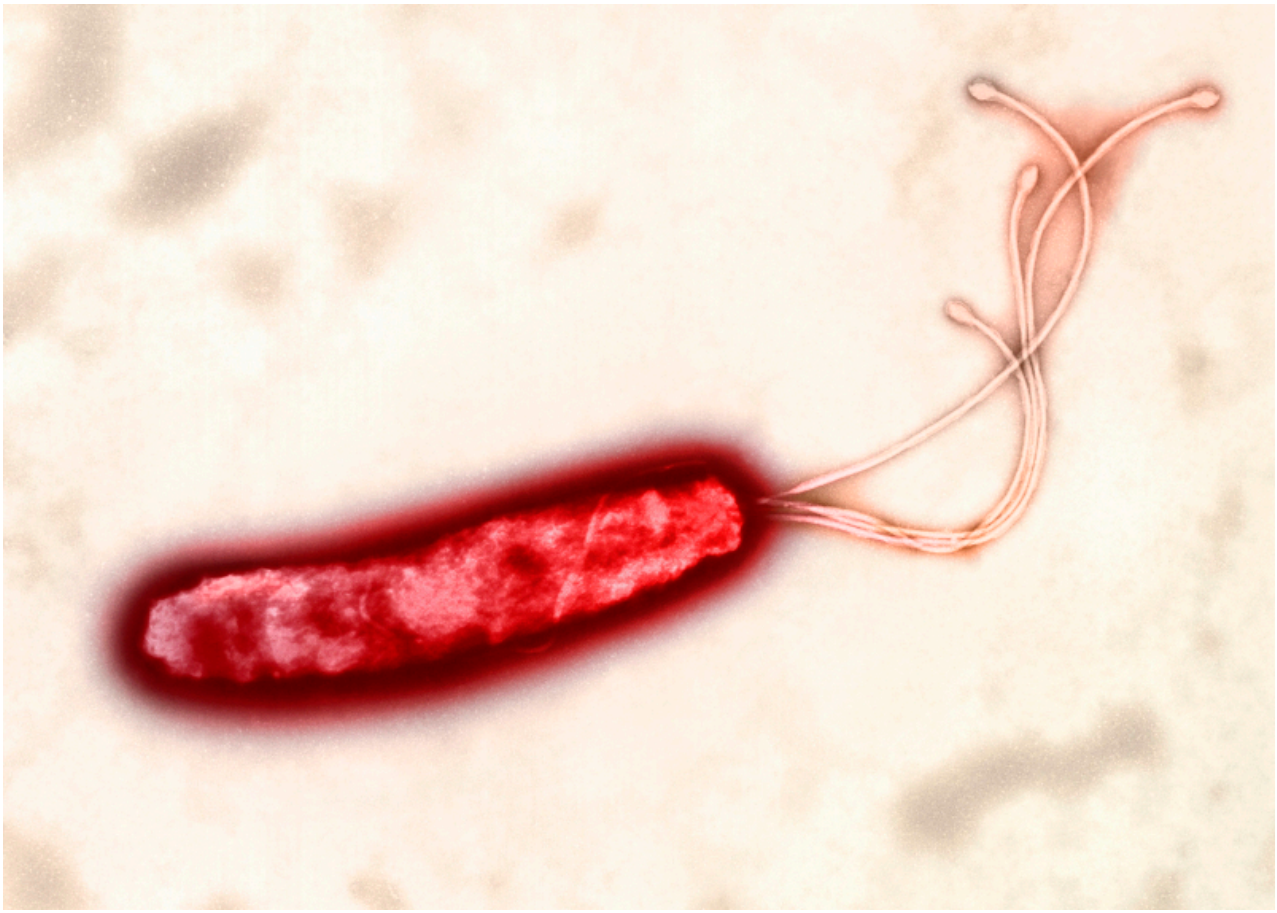

Figure 1: Helicobacter pylori bacterium, transmission electron micrograph (TEM)

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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