BMJ 2019;367:l5495 doi: 10.1136/bmj.l5495 (Published 2 October 2019)

PRACTICE

CLINICAL UPDATE

Peptic ulcer disease

Emma Sverdén *upper gastrointestinal surgeon*[1 2], Lars Agréus *general practitioner*[3] *professor*[3], Jason M Dunn *gastroenterologist*[5], Jesper Lagergren *upper gastrointestinal surgeon, professor*[1 5]

[1]Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Upper Gastrointestinal Surgery, South Hospital, Stockholm, Sweden; [3]Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [4]The University of Newcastle, Australia; [5]School of Cancer and Pharmaceutical Sciences, King's College London, and Guy's and St Thomas' NHS Foundation Trust, UK

What you need to know

- More than 90% of duodenal ulcers are linked to *H pylori* infection; eradication therapy with antibiotics and proton pump inhibitors is the mainstay of treatment
- A "test and treat" strategy for *H pylori* infection is appropriate in patients under 60 with suspected peptic ulcer disease who have no complications
- Proton pump inhibitors are important in the prevention and treatment of peptic ulcer disease, but avoid their use without clear indications, and re-evaluate patients on long-term treatment
- Gastric ulcers are followed up with endoscopy until healed to rule out malignancy
- Urgently refer patients with complications such as bleeding, perforation, or penetration to an emergency unit

Peptic ulcer disease presents with gastrointestinal symptoms similar to dyspepsia and can be difficult to distinguish clinically. It can have potentially serious complications such as bleeding or perforation, with a high risk of mortality.[1] Optimal treatment with proton pump inhibitors (PPIs) facilitates healing and can prevent complications and recurrence.

Observational studies and surveys among healthcare providers report that adherence to evidence based treatment guidelines is often poor.[2-9] This results in inadequate treatment and overuse of PPIs. Increasingly, antibiotic resistance has affected the choice of eradication regimen for *Helicobacter pylori* infection, the main risk factor. In this Clinical Update, we review the epidemiology and management of peptic ulcer disease for non-specialists to guide prompt diagnosis and appropriate treatment.

What is peptic ulcer disease?

Peptic ulcer disease is often defined as a mucosal break greater than 3-5 mm in the stomach or duodenum with a visible depth. It is therefore an endoscopic diagnosis in contrast to dyspepsia, which is a clinical diagnosis based on symptoms alone. Peptic ulcer disease results from an imbalance between factors that protect the mucosa of the stomach and duodenum, and factors that cause damage to it (fig 1).

Patients with gastric and duodenal ulcers present similarly. They may report epigastric or retrosternal pain, early satiety, nausea, bloating, belching, or postprandial distress. These symptoms are non-specific and may be difficult to distinguish clinically from functional dyspepsia. Studies have shown low correlation between symptoms and endoscopic findings.[10] Conversely, patients may be asymptomatic until a complication occurs, or an ulcer may be diagnosed incidentally during endoscopy performed for other reasons.

How common is it?

Peptic ulcer disease affects 1-2 per 1000 people annually as per a systematic review with data from the USA, UK, and Europe.[1 11 12] The incidence is declining, possibly due to decreasing prevalence of *H pylori* infection.[1 13] A time trend study from Asia (12 612 patients) showed similar incidence and declining trend.[14]

Complications from peptic ulcer disease have not fallen, however, according to a systematic review and meta-analysis (18 studies from Europe, USA, and Israel, more than 1000 individuals per study).[1] An ageing population that has more comorbidities and more frequently uses ulcerogenic medications may be contributing to this.

What are the risk factors?

Previous studies suggest that 90% of duodenal ulcers and 70% of gastric ulcers are associated with *H pylori* infection.[15 16] Although these percentages are now considered to be lower, *H pylori* is also an important risk factor for gastric cancer, which further emphasises the importance of its eradication.[17 18]

Correspondence to emma.s.eklund@gmail.com

Medications such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) cause approximately 10% of peptic ulcers. NSAIDs are more strongly linked to gastric ulcers than duodenal ulcers.[19-22] The combination of aspirin with NSAIDs further increases the risk.[23] Use of these drugs has increased over the last few decades. In the USA, self-reported use of aspirin and NSAIDs increased by 57% and 43%, respectively, between 2005 and 2010. Nearly 46% of all people over 70 were regular aspirin users in 2010, according to a national survey (27 157 people).[24] Selective COX-2 (cyclo-oxygenase-2) inhibitors have a lower risk of peptic ulcer disease compared with non-selective NSAIDs.[25]

Marginal ulcer is seen in approximately 5% of patients who have undergone gastric bypass surgery for obesity.[26] The incidence can be as high as 27-36% in patients with upper gastrointestinal symptoms after gastric bypass surgery.[27]

Box 1 lists other risk factors for peptic ulcer disease. The proportion of idiopathic ulcers has been increasing in recent years.[36] A multicentre study based in France (713 patients) found that 22% of patients with duodenal or gastric ulcer were neither infected by *H pylori*, nor using ulcerogenic drugs.[37] Between 20% and 50% of duodenal ulcers in the USA and 3-12% in Europe are negative for *H pylori*.[38] Before defining an ulcer as idiopathic, all other risk factors (box 1) should be excluded.

Box 1: Risk factors and causes of ulcers in the stomach and duodenum

- *H Pylori*
- NSAIDs
- Gastric bypass surgery
- Cigarette smoking[28]
- Selective serotonin reuptake inhibitors[29 30]
- Zollinger-Ellison syndrome (uncommon, gastrin producing tumour usually located in the pancreas)
- Physiological stress associated with serious trauma and critical illness[31] (eg, septicaemia)
- Gastric tumours mistaken for peptic ulcers
- Autoimmune diseases, eg, vasculitis, sarcoidosis, and Crohn's disease
- Infections, mainly in immunocompromised patients, eg, cytomegalovirus, tuberculosis, and syphilis[32]
- Psychological stress is not an established risk factor for peptic ulcer disease, although some research has suggested an association[33]
- Consumption of alcohol or coffee does not seem to increase the risk of peptic ulcer disease[34 35]

What are the complications?

Bleeding, perforation, penetration to a surrounding organ, and obstruction from fibrotic stricturing (usually in the pyloric region) are important complications. Box 2 lists signs suggestive of acute bleeding. Perforation usually presents with acute onset of severe abdominal pain. Penetration can cause secondary pancreatitis if the pancreas is involved. Obstruction causes nausea and vomiting.

Box 2: Red flags for referral to a specialist

- Signs of acute bleeding[39 40]:
  - Melaena, self-reported or found on digital rectal examination
  - Blood in vomit (haematemesis)
  - Abnormally high pulse or low blood pressure
  - Severe anaemia
- Signs of perforation or penetration such as severe abdominal pain and peritonitis
- Symptoms suggestive of malignancy in patients over 50:
  - o Dysphagia[41]
  - o Unexplained weight loss with upper abdominal pain or gastro-oesophageal reflux
  - o Loss of appetite
  - o Recurrent vomiting
  - o Anaemia
- Second line eradication therapy fails
- Symptoms persist despite successful eradication

Bleeding peptic ulcer occurs in 19 to 57 per 100 000 individuals each year, as per a systematic review (93 studies). Perforation or penetration is relatively less common, occurring in 4 to 14 per 100 000 individuals each year.[42] The risk of recurrence and complications from idiopathic ulcers is higher than for ulcers with known aetiology, as reported in prospective cohort studies.[43 44] Mortality is high with these complications. About 8.6% of patients with peptic ulcer bleeding and 23.5% of patients with perforation die within 30 days.[42]

What to cover on initial assessment?

Ask about the nature of symptoms and risk factors such as previous ulcer disease, other medical conditions, medications, and smoking. Inquire about symptoms suggestive of complications listed in box 2.

On examination, record pulse and blood pressure. Severe peptic ulcer bleeding may affect the patient's haemodynamic status. Palpate the abdomen. Pronounced tenderness may suggest perforation or penetration, indicating the need for emergency referral. Assess for any palpable mass which may represent malignancy. Digital rectal examination is useful to detect melaena when bleeding from a peptic ulcer is suspected.

When to refer?

Box 2 lists features that prompt referral. Immediately transfer patients with signs of bleeding or perforation to an emergency unit. Refer patients with symptoms suggestive of malignancy to a specialist gastroenterology unit for urgent endoscopy within two weeks.

What investigations can be done?

Request a blood test to detect anaemia. Endoscopy is required to confirm ulcer diagnosis, but may be avoided in patients under 55 with no complications.

Testing for *H pylori*

Current guidelines recommend a "test and treat" strategy for *H pylori* in patients with symptoms suggestive of peptic ulcer disease and ≤55 years (National Institute for Health and Care Excellence)[39] or ≤60 years (American College of Gastroenterology).[45 46] Non-invasive tests include urea breath test, stool antigen test, or serology. The urea breath test delivers an immediate result and can be performed at home with the necessary equipment. A stool antigen test is equally reliable,

and the stool sample can be collected at home. Serology testing for antibodies has high sensitivity but low specificity, ie, a negative test excludes infection, but a positive result needs to be confirmed by another test. It cannot be used to confirm eradication.

Unlike the serology test, a single negative urea breath test or stool antigen test does not exclude *H pylori* infection. Bleeding or use of PPIs and antibiotics might cause false negative results. Discontinue PPIs for two weeks[47] and antibiotics for at least four weeks before testing.[48] If no other probable cause of the ulcer is identified, repeat testing a few weeks later.

Endoscopy

Endoscopy is advised in older people with dyspepsia, in patients with red flag symptoms (box 2),[39] and in patients whose dyspeptic symptoms do not resolve after 4-8 weeks of PPI. Whether endoscopy should be used more liberally in patients with diffuse upper gastrointestinal symptoms is debated.[49] At endoscopy, *H pylori* can be diagnosed by rapid urease test or on histology, both of which are invasive tests.

Additional specialist tests can include platelet cyclo-oxygenase activity or blood salicylic acid to establish any link to the use of NSAIDs or aspirin, and fasting gastrin to exclude Zollinger-Ellison syndrome, before determining an ulcer as idiopathic.

How is it managed?

The initial management is usually acid suppressing treatment along with elimination of risk factors.

Acid suppression

Endoscopically confirmed peptic ulcers without *H pylori* infection are treated with a PPI until healed, along with elimination of any other known risk factors. Systematic reviews have shown that PPIs accelerate the healing process and facilitate eradication of *H pylori*.[50-52] The odds of ulcer healing were three times higher with PPIs compared with control group (odds ratio 3.49, 95% confidence interval 3.28 to 3.72) in a recent meta-analysis (847 randomised trials, 142 485 participants).[50] For duodenal ulcers, when *H pylori* is the predominant cause, acid suppression included in the eradication therapy for 7-14 days is usually sufficient for healing. Gastric ulcers are treated with acid suppression until healing is confirmed on repeat endoscopy.

The duration of acid suppression for the test and treat recommendation (without prior endoscopy) differs between guidelines, but no more than eight weeks is recommended. Reassess the patient after 4-8 weeks for resolution of symptoms.[45]

We advise caution against overuse of PPIs. Ensure that the treatment is clearly indicated with adequate dosage. Re-evaluate the indication for any continued treatment. Observational studies in different settings suggest that between 27 and 81% of PPI use in primary care and 36-63% of use in hospitals could be inappropriate,[2 53 54] ie, having no documented indication for its use or prescribed without re-evaluation. Approximately half of older patients in primary care using NSAIDs were prescribed higher than therapeutic doses or double dose regimens of PPIs in a national audit in Bahrain.[55] This overuse results in unnecessary healthcare costs and an increased risk of adverse effects, such as hip fracture,[56] cardiovascular events,[57] *Clostridium difficile* infection, pneumonia, dementia,[58] and gastric cancer in long term users.[59 60] The evidence regarding these side effects is largely derived from observational studies, with a risk of confounding,[61] but the potential harms need to be considered in the scenario of overuse and long term use.

Consider alternatives such as histamine 2 receptor antagonists if patients experience side effects. Misoprostol, a prostaglandin analogue, is effective in treating and preventing ulcer recurrence, but compliance is poor owing to side effects such as diarrhoea, nausea, and abdominal pain.[62]

H pylori eradication

Patients testing positive for *H pylori* should receive eradication therapy.[39 45 63 64] The choice of antibiotics is determined by antibiotic resistance patterns in any geographical region. Figure 2 describes typical eradication regimens. Patients can find eradication regimens challenging to follow because they involve talking multiple drugs at the same time. Offer clear written explanation if they would prefer.

Regimens with eradication rates of ≥90% are recommended. In northern Europe, which has a low prevalence of clarithromycin resistant *H pylori*, "triple therapy" is recommended. This is a combination of two antibiotics and a PPI twice daily for 7-14 days depending on empirical efficacy in the region. In many regions, for example Italy, Japan, Turkey, and China, this provides an unacceptably low eradication rate, often <80%.[65] In populations with higher prevalence of antibiotic resistance, expert consensus suggests that a "quadruple therapy" is appropriate. This can be concomitant (14 days) or sequential (7+7 days) (fig 2).[66 67] Bismuth is a bactericidal salt that can be added to the quadruple regimen. Prolonged triple therapy in higher doses is an alternative to quadruple regimens.[65]

Medication related peptic ulcer disease

Along with prescribing PPIs, consider whether NSAIDs can be discontinued in the patient. A COX 2-selective NSAID in combination with a PPI may be preferred in these patients. The risk of cardiovascular complications has long been considered to be more pronounced with the COX-2 selective NSAID, but a recent review reports similar cardiovascular risk across NSAIDs.[25 68] Use of low dose aspirin for prevention of cardiovascular events can be continued in combination with a PPI.[69 70]

Some patients may require long term acid suppression if using ulcerogenic drugs for a longer duration (box 3). Patients are often uncertain of the reason for long term treatment with PPIs and may not be aware that NSAIDs and aspirin can cause peptic ulcer disease. Educate patients about these risks so they are compliant with the treatment.

Box 3: Indications for long term therapy with a PPI in long term users of aspirin or NSAIDs[71]

- Age >65 years
- A history of peptic ulcer disease, especially with complications
- NSAID use at high doses or in combination with certain other drugs, ie, aspirin, steroids, selective serotonin reuptake inhibitors, or anticoagulants
- Aspirin use, even at low dosage in elderly patients, particularly in combination with drugs listed above

Histamine 2 receptor antagonists are effective in preventing duodenal ulcers among NSAID users, but not gastric ulcers.[72] These have a shorter duration of action and do not completely suppress postprandial secretion of gastric acid,[73] which requires at least twice-daily dosage. Randomised trials and cohort studies

have shown that high doses of famotidine (80 g daily) prevent gastric ulcers, although not as effectively as PPIs.[74]

Marginal ulcer

There is no evidence based treatment of marginal ulcers, and they are often difficult to heal.[26] Eliminate any risk factor and consider a high dose PPI regimen.[75] Follow up with endoscopy until the ulcer is healed.

Managing complications

In patients with peptic ulcer bleeding, endoscopic treatment reduces the risk of re-bleeding, the need for surgery, and mortality.[40 76] Approximately 10% of patients require urgent angiographic embolisation or surgery for bleeding despite endoscopic intervention.[77]

The gold standard treatment of ulcer perforation is surgery. Endoscopic stenting plus drainage is a less invasive alternative, but its role is debated.[78] Pyloric obstruction is typically managed endoscopically with dilatation, although surgery is sometimes required.[79]

What to cover at follow-up visits?

Ask the patient about improvement in symptoms. Assess outcome of eradication therapy, preferably non-invasively, eg, by a urea breath test or a stool antigen test, at least 2 weeks after finishing the PPI therapy. More than 85% of patients experience eradication with good compliance to treatment when the prescription is appropriate for the local resistance pattern. Discuss elimination of other risk factors—mainly NSAIDS and smoking.

Patients with a confirmed endoscopic diagnosis of duodenal ulcer do not require follow-up after eradication. Patients with gastric ulcers will need repeat endoscopies and biopsies until confirmed healed, mainly because such ulcers are slower to heal and some may actually be gastric cancers misdiagnosed as an ulcer. Continue PPI treatment after eradication for up to 8 weeks in total or until healing is endoscopically confirmed.[80] Of note, a malignant ulcer can also temporarily heal with PPI treatment, so biopsies must also be sampled from any visible scar tissue.[81] *H pylori* eradication may not completely eliminate the risk of gastric cancer. Expert consensus is to offer endoscopic and histological surveillance in patients at risk—as defined by the extent and severity of mucosal atrophy on endoscopy.[82]

If eradication fails, second line therapy should be tried (fig 2). If there is no response on second line therapy, or if symptoms persist despite successful eradication, refer the patient to a specialist. Culture from a biopsy of the gastric mucosa can determine potential antibiotic resistance.

Education into practice

- Think about a patient with dyspeptic symptoms you have seen in your practice recently. How would you alter your management approach based on reading this article?
- How many patients at your practice are on long term treatment with NSAIDs or aspirin and PPIs? When has their indication for continued treatment been evaluated?

Questions for future research

- What strategies are effective in treating patients with *H pylori* antibiotic resistance?
- What are the adverse effects of PPI, especially potential cancer risk, with long term use or higher doses?
- Which is the ideal long term strategy to prevent recurrence of peptic ulcer disease in high-risk individuals?
- How can marginal ulcers occurring after gastric bypass surgery for obesity be prevented and treated?

Additional educational resources

- The American College of Gastroenterology https://gi.org/guideline/management-of-dyspepsia-2/
- The European Society of Gastrointestinal Endoscopy https://www.esge.com/assets/downloads/pdfs/guidelines/2015_s_0034_1393172.pdf
- The National Institute for Health and Care Excellence (NICE)
- https://www.nice.org.uk/guidance/cg184https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#upper-gastrointestinal-tract-cancers

Information resources for patients

National Institute for Health and Care Excellence (NICE) public information. https://www.nice.org.uk/guidance/cg141/ifp/chapter/About-this-information

How patients were involved in the creation of this article

No patients were involved in the creation of this article.

How this article was created

We searched PubMed using the term “peptic ulcer.” We prioritised systematic reviews and high quality and recently published original studies on the topic. We excluded animal and paediatric studies. We also reviewed clinical guidelines from the American College of Gastroenterology, the European Society of Gastrointestinal Endoscopy, the National Institute for Health and Care Excellence, and the Japanese Society of Gastroenterology.

Competing interests *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: none.

Further details of The BMJ policy on financial interests is here: https://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests

Provenance and peer review: commissioned; externally peer reviewed.

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Figures

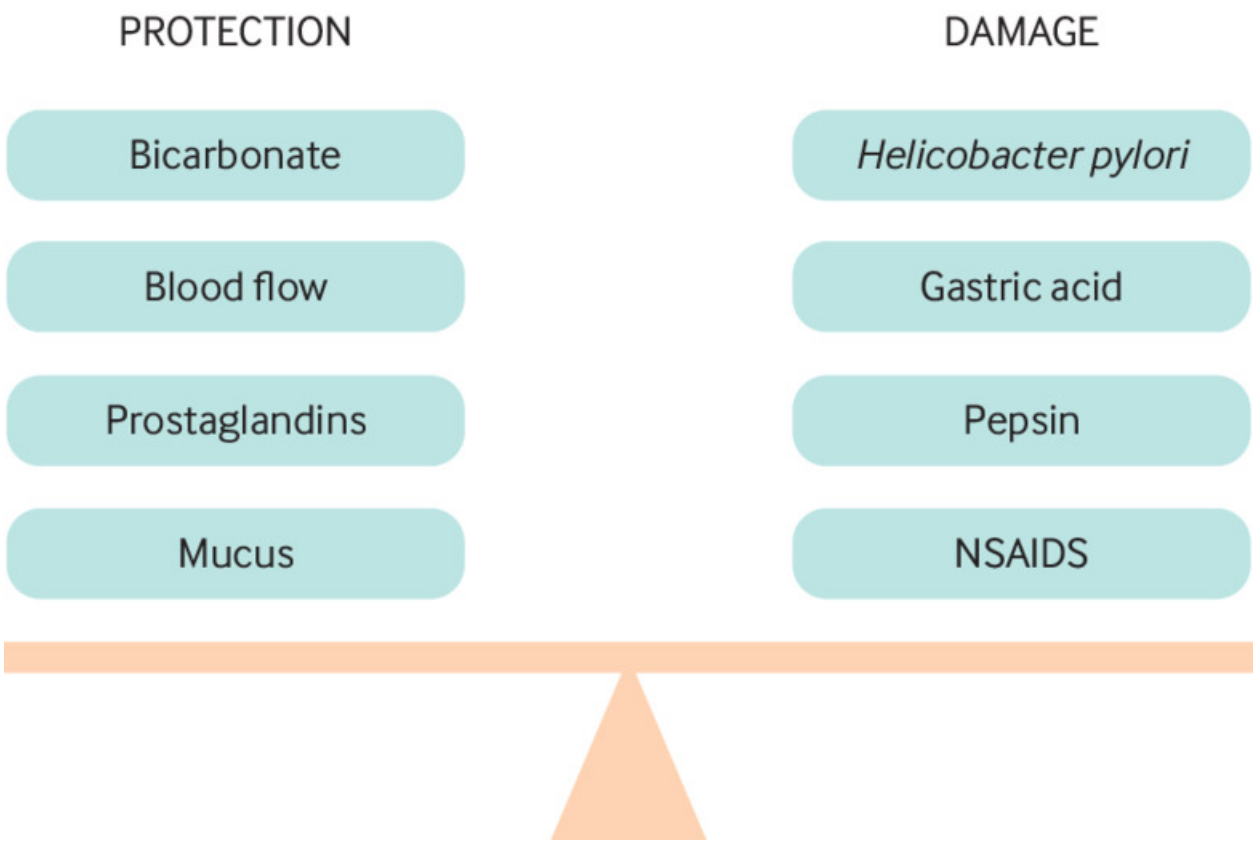
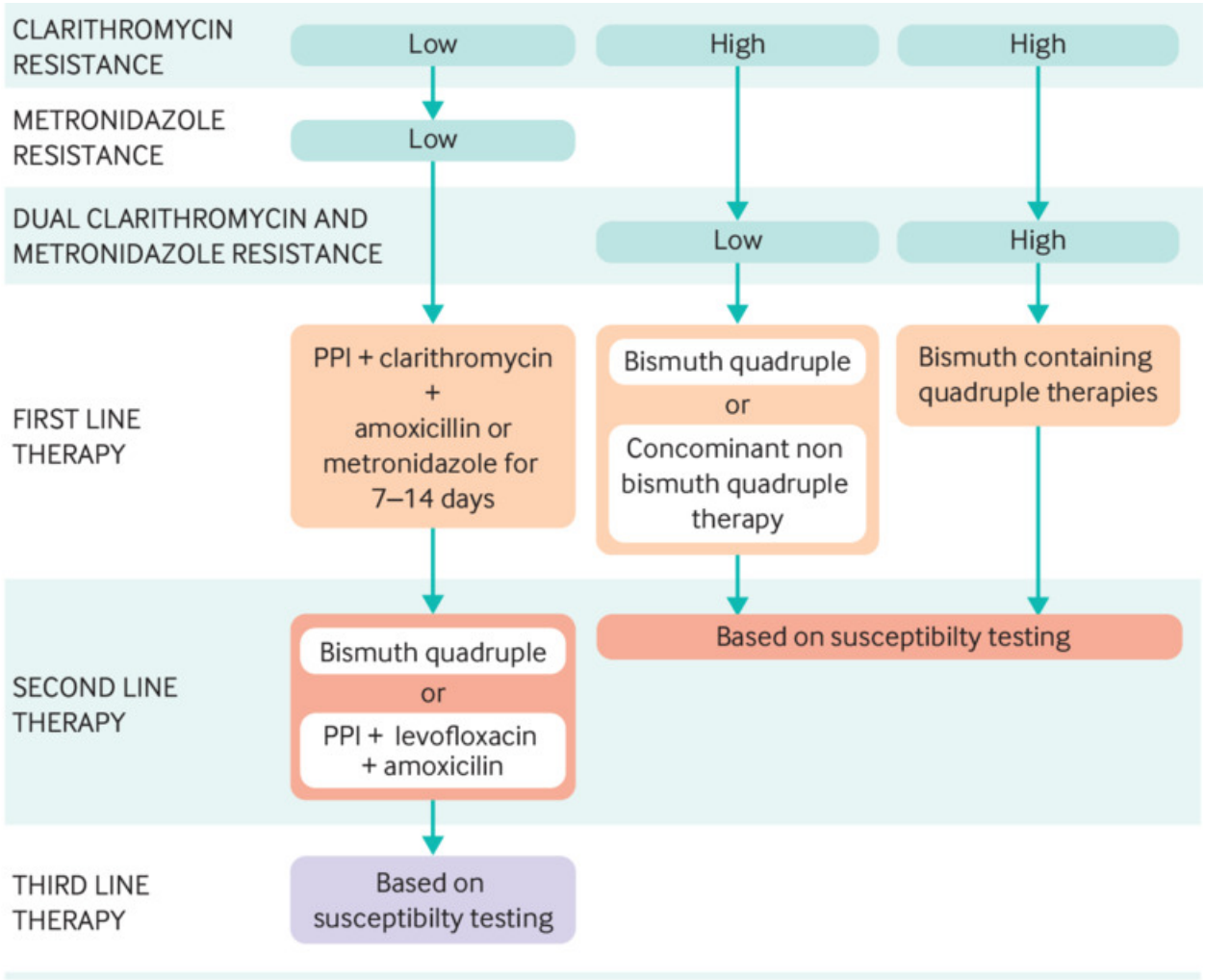


Fig 1 Factors that protect or harm the gastroduodenal mucosa



Bismuth is a salt with bactericidal effect

Bismuth quadruple is the triple therapy regimens with bismuth added in

Triple therapy: proton pump inhibitor plus two different antibiotics

Quadruple therapy: proton pump inhibitor plus three different antibiotics

Sequential therapy: for example first 7 days proton pump inhibitor plus amoxicillin, next 7 days proton pump inhibitor plus clarithromycin plus metronidazole

Concomitant therapy: for example simultaneously proton pump plus amoxicilin, clarithromycin and metronidazole for 10 days

Fig 2 Regimens for eradicating *H pylori*