Peptic Ulcer Disease in Older People
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ABSTRACT
Peptic ulcer disease is a common disorder that affects millions of people worldwide. When complications occur, peptic ulcer disease can have a major impact on quality of life and on the utilisation of the health system. Understanding the causative roles of Helicobacter pylori and non-steroidal anti-inflammatory drugs has led to changes in management of the disease. Comorbidities in older people add further complexity to treatment. This article summarises the clinical aspects of peptic ulcer disease and outlines principles which enable effective treatment.


INTRODUCTION
The Nobel Prize in Physiology or Medicine 2005 was awarded jointly to Barry J Marshall and J Robin Warren ‘for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease’.1,2 Awarding of this prestigious prize highlighted the importance of peptic ulcer disease and the potential for improving clinical outcomes and decreasing healthcare costs.

Older people comprise an increasing proportion of most Western societies. Peptic ulcer disease has a major impact on the health system and continues to be a considerable cause of patient morbidity and mortality. The past decade has seen the introduction of new anti-inflammatory drugs, which theoretically should cause fewer peptic ulcers. The greater use of aspirin from the increasing awareness of its positive role in vascular disease prevention has increased the risk of peptic ulcer disease. The increasing use of non-aspirin anti-thrombotic drugs also contributes to the risk of gastrointestinal bleeding – the most frequent and life-threatening complication of peptic ulcers. Therefore, an improved understanding of peptic ulcer disease offers the opportunity to prevent occurrence and implement effective treatment.

AETIOLOGY
Peptic ulcers are defects of the gastrointestinal mucosa that extend through the muscularis mucosa because of the presence of acid and pepsin. A peptic erosion is a similar defect that is superficial and does not penetrate the muscularis mucosa. However, a peptic erosion cannot always be distinguished from a peptic ulcer at endoscopy and the two conditions often coexist. The principal causes of peptic ulcers are Helicobacter pylori infection, and the use of non-steroidal anti-inflammatory drugs (NSAID) and aspirin. Smoking and excessive alcohol intake also increase the risk of peptic ulcer disease. Age is another risk factor, possibly a reflection of escalating H. pylori infection and altered mucosal resistance.

Peptic ulcer disease is the cause of significant morbidity with patients having a low health-related quality of life. Gastric bleeding is a common initial presentation and complications include perforation, penetration and gastric outlet obstruction. The healthcare costs of complicated peptic ulcer disease are considerable; often requiring emergency endoscopy, hospital admission and surgery.3

Non-Steroidal Anti-Inflammatory Drugs
The incidence of peptic ulcers in NSAID users during endoscopy is around 20% and this incidence increases linearly with age. It is estimated that over 50% of NSAID use is in people over 60 years, of whom approximately 15% take these analgesics. NSAID use is frequently associated with gastric ulcers, or with bleeding gastric or duodenal ulcers.4

Cyclo-oxygenase-2 selective (COX-2) inhibitors are possibly safer than conventional (non-selective) NSAID. However, one large study demonstrated that the risk of adverse upper gastrointestinal events increased in both COX-2 inhibitor and non-selective NSAID users.5 Overall, the incidence of adverse events was 1.4 per 100 person years.6 The risk of adverse upper gastrointestinal events was significantly higher for naproxen, diclofenac and rofecoxib (OR 1.6 to 2.1) but not celecoxib. The use of ulcer healing drugs reduces the risk of peptic ulcer disease except when used in conjunction with diclofenac.7

The risk of bleeding from peptic ulcer disease in non-selective NSAID users is approximately 5-fold but less for COX-2 inhibitors.8 The risk of bleeding from the upper gastrointestinal tract depend on a variety of factors, such as:
• history of previous complicated ulcer (OR 14);
• multiple NSAID use (including aspirin) (OR 8.9);
• high-dose NSAID (OR 7);
• anticoagulant therapy (OR 6.4);
• previous uncomplicated ulcer (OR 6.1);
• age over 70 years (OR 5.6);
• H. pylori infection (OR 3.5); and
• oral corticosteroids (OR 2.2).8

Gastrointestinal bleeding may be secondary to a drug’s antiplatelet effect, which is supported by the finding that clopidogrel also increases the risk of upper gastrointestinal bleeding without ulceration. The combination of low-dose aspirin with esomeprazole has a lower rate of gastrointestinal bleeding than clopidogrel alone.9
Increased risk of ulcer bleeding has also been reported in users of selective serotonin reuptake inhibitors. This risk is amplified by concomitant NSAID use. This mechanism of action is not understood.6,8 Co-therapy with proton pump inhibitors reduces the risk of NSAID-induced ulcers. Histamine H₂-receptor antagonists, by comparison, are less effective. In one study, diclofenac plus omeprazole was as safe as celecoxib alone. Another study reported that celecoxib and esomeprazole caused less gastrointestinal bleeding than celecoxib alone (5% vs 8.9% in 12 months).11 The latter study suggests that there is a small but definite risk of gastrointestinal bleeding when taking COX-2 inhibitors.

**Aspirin**

Low-dose aspirin increases the risk of gastrointestinal bleeding 2-fold. The risk is higher in users with a history of previous complicated ulcer, advanced age and concomitant use of corticosteroids, NSAID, clopidogrel or anticoagulants.12 Histamine H₂-receptor antagonists are effective in preventing aspirin-induced injury; however, proton pump inhibitors are more efficacious.13 Aspirin and COX-2 inhibitor users have a 28% reduced risk of bleeding compared with aspirin and non-selective NSAID users.14 This bleeding risk must be weighed up with the benefits of aspirin in primary prevention of cerebrovascular and coronary events.

**Helicobacter pylori Infection**

*H. pylori* infection is the leading cause of peptic ulcer disease. Nearly all duodenal ulcers and up to two-thirds of gastric ulcers are *H. pylori* positive. An increasing prevalence of infections with age portends more *H. pylori* positive ulcers in older people. The debate about the exact causative mechanism of *H. pylori* infection continues; nevertheless effective eradication therapy has led to the cure of peptic ulcer disease.15,16

Endoscopic and non-invasive diagnostic testing is widely available. While ‘test then treat’ strategies, usually general practitioner initiated non-invasive diagnostic testing, are widely advocated for younger patients, the preferred approach in older patients is to establish an accurate diagnosis before starting treatment.17 This is as new symptoms in older patients, especially alarm symptoms, such as anaemia, dysphagia/odynophagia, bleeding, vomiting, weight loss and anorexia, warrant endoscopy.

The incidence of *H. pylori* resistance to clarithromycin is increasing with a resultant reduction in the efficacy of standard eradication treatments. No longer are these eradication treatments 90 to 95% successful and alternative regimens have been proposed.18

Opinions vary as to whether NSAID are independent risk factors or synergistic with *H. pylori* for gastrointestinal bleeding risk, particularly in older patients.19,20 Regardless of whether NSAID and *H. pylori* interact, the combination is frequently encountered and managing both reduces subsequent ulcer risk.8 While gastrointestinal symptoms may alert the clinician to peptic ulcer disease, many patients are asymptomatic. Complications such as bleeding are often the first presentation of NSAID-related ulcers.6,8 Prompt recognition will assist early hospital admission for appropriate management.

Despite a decrease in the incidence of peptic ulcer bleeding, the rate of mortality has not diminished. Hospitalisation rates remain high for elderly NSAID users (new and long-term users) and range from 12 to 22 per 1000 person-years.21 Deaths in this situation are often due to comorbidities.22

**PREVENTION**

It is essential to identify individuals at greatest risk of peptic ulcer disease or upper gastrointestinal haemorrhage. Preventive strategies are most likely to benefit patients with:

- previous history of ulcers (particularly complicated);
- multiple NSAID use (including aspirin);
- high-dose NSAID use;
- anticoagulant therapy;
- age over 70 years;
- *H. pylori* infection; and
- oral corticosteroid use.

Therefore, avoiding NSAID, decreasing the NSAID dose, or COX-2 inhibitor use may reduce the risk of complications.

Co-therapy with proton pump inhibitors in low-dose aspirin or NSAID users is the most effective means of preventing peptic ulcer disease in high-risk individuals. Histamine H₂-receptor antagonists are also effective in some situations, but less so than the proton pump inhibitors.12,13

Empirical *H. pylori* eradication is standard treatment for duodenal ulcers. Screening is not routine, except in populations with a high incidence of gastric cancer. In 2008, the Asia-Pacific Consensus Conference recommended that: ‘*H. pylori* infection should be tested for and eradicated … prior to long-term aspirin or non-steroidal anti-inflammatory drug therapy in patients at high risk for ulcers and ulcer-related complications’.21 This is especially true for gastric ulcers, where it is standard practice to test for *H. pylori* infection prior to antibiotic therapy.

**MANAGEMENT**

The principles of management for peptic ulcer disease are straightforward and include:

- accurate diagnosis, usually endoscopic, to exclude malignancy and assess *H. pylori* status;
- treating the cause, i.e. treat *H. pylori* if present and cease causative drug;
- early recognition of complications, with appropriate intervention as required, e.g. endoscopic or surgical;
- management of comorbidities (important to improve outcomes);
- healing the ulcer; and
- repeat endoscopy to verify healing of gastric and complicated duodenal ulcers.

**Complicated Peptic Ulcers**

Endoscopic intervention within 24 hours of presentation reduces the duration of hospital stay in older people with gastrointestinal bleeding.24 Once endoscopic haemostasis has been achieved, re-bleeding is greatly reduced by treatment with intravenous or high-dose oral proton pump inhibitors.25,26 Generally, 15% to 20% of patients re-bleed within the first 3 days. In a recent series, overall mortality secondary to peptic ulcer bleeding ranged from 4% to 12% and when the bleeding recurred, the mortality was 10 times higher.25
Ideally, all NSAID should be ceased and consideration given to substituting non-selective NSAID with COX-2 inhibitors. To heal peptic ulcers, patients should be treated with either proton pump inhibitors or histamine H₂-receptor antagonists. If aspirin or NSAID cannot be ceased, co-therapy with proton pump inhibitors is more effective than histamine H₂-receptor antagonists (Tables 1 and 2).

### Table 1. Proton pump inhibitor doses for peptic ulcer disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard doses</th>
<th>Higher doses</th>
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<tbody>
<tr>
<td>Esomeprazole</td>
<td>20 mg daily</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg daily</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg daily</td>
<td>20 mg twice daily  or 40 mg daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg daily</td>
<td>40 mg twice daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg daily</td>
<td>20 mg twice daily</td>
</tr>
</tbody>
</table>

If patients test positive for *H. pylori* infection, it is imperative that *H. pylori* be eradicated. In Australia, *H. pylori* eradication is recommended for 7 days with esomeprazole + amoxicillin + clarithromycin (Nexium Hp7, Klacid Hp7) – the only combination available on the Pharmaceutical Benefits Scheme (Table 3).

### Table 2. Histamine H₂-receptor antagonist doses for peptic ulcer disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard doses</th>
</tr>
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<tbody>
<tr>
<td>Famotidine</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>150 mg twice daily</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>150 mg twice daily</td>
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When clarithromycin resistance is suspected or eradication is not successful, a variety of alternative treatments have been proposed. The Asia-Pacific Consensus Conference concluded: ‘There appears to be an increasing rate of resistance to clarithromycin and metronidazole in parts of Asia, leading to reduced efficacy of proton pump inhibitor-based triple therapy. There are insufficient data to recommend sequential therapy as an alternative first-line therapy in Asia. Salvage therapies that can be used include: (i) standard triple therapy that has not been previously used; (ii) bismuth-based quadruple therapy; (iii) levofloxacin-based triple therapy; and (iv) rifabutin-based triple therapy.’

Some of these drugs (e.g. bismuth, tetracycline, furazolidone) are available in Australia via the Special Access Scheme, while rifabutin availability is restricted. These treatments can be expensive and their evaluation is not complete.

Older patients are able to tolerate *H. pylori* eradication treatments with limited adverse effects. However, if compliance may be an issue, a dose administration aid prepared by pharmacy may be of benefit.

### CONSIDERATIONS

#### Ulcer Bleeding with Low-Dose Aspirin

If patients experience ulcer bleeding while on low-dose aspirin, prescribers are often in a quandary about whether the aspirin should be ceased or therapy continued with a proton pump inhibitor. It is necessary to weigh up the cardiovascular and gastrointestinal risks of individual patients. As aspirin has ulcerogenic and antiplatelet effects, it is not surprising that a recent study concluded that continuing aspirin in patients who bleed from peptic ulcer disease may increase the risk for recurrent bleeding but this may potentially reduce mortality rates.

Some studies have suggested that cardiovascular events or reduced drug efficacy are more frequent in clopidogrel users who take a proton pump inhibitor (often to reduce ulcer/bleeding risk from concomitant aspirin or NSAID use). This increased risk has not been reported with pantoprazole.

Several authors have urged caution in drawing conclusions from such studies, because they were uncontrolled for important confounding factors, particularly comorbidities or were not randomised. Laine and Hennekens concluded that there was no difference in cardiovascular events in those on both clopidogrel and proton pump inhibitors.

Nevertheless, the US Food and Drug Administration has issued an alert for health professionals about a drug interaction between clopidogrel and omeprazole and urge caution in this situation. Some go further and claim that current evidence does not justify a conclusion that proton pump inhibitors are associated with cardiovascular events among clopidogrel users. *Ex-vivo* studies of platelet function may or may not be related to a clinical endpoint in patients. The authors add that changing to another proton pump inhibitor or histamine H₂-receptor antagonists is not supported by any randomised study.

Another consideration may be to switch the low-dose aspirin for clopidogrel. A study from Hong Kong reported that clopidogrel use was associated with more than 10 times the risk of ulcer bleeding compared with low-dose aspirin plus esomeprazole use. Yet, many recommend clopidogrel in this situation.

### FUTURE

Peptic ulcer disease in older people is complex, not just because ulcer disease is multifactorial with different treatments, but because older people have numerous comorbidities, and their regular medications may interact with the drugs used to treat or prevent ulcers and their complications.

The future should see tailoring of therapy to patients’ risk categories, i.e. ulcer disease recurrence, gastrointestinal bleeding, and cardiovascular.

**Competing interests:** None declared

**References**


