

## Review article: management of peptic ulcer bleeding—the roles of proton pump inhibitors and *Helicobacter pylori* eradication

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### SUMMARY

Peptic ulcer bleeding is associated with substantial morbidity and mortality. The goals of management are to control any active bleeding and prevent re-bleeding and then to heal the ulcer and prevent its recurrence. Initial management strategies are guided by the patient's clinical condition and endoscopic findings. Thus, treatment may consist of endoscopic and medical therapy and, sometimes, surgery. Control of acid secretion, preferably with proton pump inhibitor therapy in the initial management continues to evolve; it has also been used as both an adjunct to endoscopic therapy and as primary treatment. These agents have

been found to be effective in some trials in the reduction of re-bleeding and the need for surgery, although there is no clear benefit demonstrated for overall mortality. Proton pump inhibitors have been administered either intravenously or orally in different trials. The long-term management of patients with peptic ulcer, after the initial bleeding episode, should include patient stratification based upon risk factors for ulcer recurrence (i.e. *Helicobacter pylori* infection, use of aspirin or nonsteroidal anti-inflammatory drugs). Elimination or modification of these risk factors reduces the risk of ulcer recurrence and, hence, of recurrent ulcer bleeding.

### INTRODUCTION

Peptic ulcer bleeding is a potentially life-threatening event that accounts for a substantial number of hospitalizations and appreciable patient mortality in all Western countries. Data from Europe indicate that between 10 and 50 of every 100 000 hospitalizations are due to upper gastrointestinal bleeding,<sup>1</sup> with US epidemiological data supporting these numbers.<sup>2</sup> In the USA, peptic ulcer remains the single commonest cause of upper gastrointestinal (GI) tract bleeding, resulting in

hospitalization with mortality rates of between 7% and 10%.<sup>2</sup> Mortality rates are higher after ulcer re-bleeding.

Factors indicating severe haemorrhage or increased risk for further haemorrhage include: haemodynamic instability on presentation, bleeding manifested as repeated haematemesis or haematochezia, and failure of the gastric aspirate to clear with lavage.<sup>3</sup> An age of more than 60 years and the presence of serious concomitant medical illness are also poor prognostic factors following an acute episode of peptic ulcer haemorrhage.<sup>3</sup> While these clinical characteristics are important for predicting patient outcome, the endoscopic appearance of the ulcer is critical. Ulcers larger than 1 or 2 cm, those with active bleeding, and those associated with a nonbleeding visible vessel have the greatest risk of re-bleeding and mortality.<sup>3</sup> The main

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goals of endoscopic management are the cessation of any active bleeding and the prevention of re-bleeding. Subsequent long-term management goals are ulcer healing and the prevention of ulcer recurrence.

#### MANAGEMENT STRATEGIES FOR BLEEDING ULCERS

The initial management of upper gastrointestinal tract bleeding consists of an assessment of the degree of blood loss with appropriate resuscitative and supportive measures as indicated. Endoscopic evaluation should determine whether ulcer disease is the source of haemorrhage. Further treatment is then driven by the endoscopic findings and may include endoscopic haemostatic therapy (with electrocoagulation, heater probe application, or injection tamponade with saline, saline with vasoactive ingredients or fibrin) and specific medical therapy (including treatment with anti-secretory agents). Endoscopic haemostatic therapy is of paramount importance for ulcers with active arterial bleeding, oozing of blood or the presence of a nonbleeding visible vessel. The optimal management of recently bleeding ulcers found to have an adherent clot in their base remains controversial. Although a recently published study reported a significantly lower rate of re-bleeding in patients with an adherent clot in an ulcer base who were treated with combination endoscopic therapy (0/15) compared with medical therapy alone (6/15;  $P = 0.011$ ),<sup>4</sup> the strength of the study conclusions may have been limited by an imbalance of risk factors at randomization, a relatively small sample size, and the investigators' subjective assessment of the end-point of re-bleeding.<sup>2</sup> Surgical therapy is generally reserved for those patients in whom endoscopic therapy fails or is unavailable.

#### ENDOSCOPIC INTERVENTION

Endoscopic techniques have virtually replaced surgical intervention in the initial management of most patients with ulcer bleeding. Upper endoscopy can identify the bleeding site, risk-stratify the chances of recurrent bleeding and control acute bleeding. Endoscopic haemostasis therapy; thermal contact devices, laser treatment and injection therapy, reduced the rates of re-bleeding (odds ratio, OR = 0.38), need for surgery (OR = 0.36) and mortality (OR = 0.55).<sup>5</sup>

In patients with initial endoscopic control of bleeding, there is some debate regarding the appropriateness and

timing of follow-up endoscopy as well as optimal pharmacologic management. A planned follow-up or 'second look' endoscopy after endoscopic haemostatic therapy may prevent some re-bleeding episodes. Marmo *et al.*<sup>6</sup> found that routine 'second look' endoscopy with re-treatment as appropriate, significantly reduced the risk of recurrent bleeding, but did not substantially reduce the rates of surgery or mortality. The absolute risk reduction in re-bleeding was 6.2% ( $P < 0.01$ ). Absolute risk reductions for surgery and mortality were, respectively, 1.7% and 1.0% ( $P = \text{N.S.}$ ). The strategy of 'second look' endoscopy with re-treatment when appropriate significantly reduced the risk of recurrent bleeding (OR = 0.64; 95% CI: 0.44–0.95;  $P < 0.01$ ), with a number needed to treat (NNT) of 16. Thus, 'second look' endoscopy has failed to prove that it has an effect on key outcome parameters such as need for surgery or mortality.

#### PHARMACOLOGICAL THERAPY

Gisbert and colleagues evaluated 11 comparative randomized trials and found proton pump inhibitor therapy to be more effective than treatment with a histamine H<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA) in the prevention of recurrent bleeding from peptic ulcer. The therapies were comparable in their reduction of need for surgery and patient mortality.<sup>7</sup> In patients not undergoing endoscopic therapy, persistent or recurrent bleeding was less frequent in those treated with a proton pump inhibitor rather than with an H<sub>2</sub>RA (4.3% vs. 12%; OR = 0.24). In those who received endoscopic therapy, the difference was less marked (10.3% with a proton pump inhibitor vs. 15.2% with an H<sub>2</sub>RA).

In an early study of oral proton pump inhibitor therapy, Khuroo and colleagues<sup>8</sup> treated 220 patients with duodenal, gastric or stomal ulcers and endoscopic signs of recent bleeding (26 with arterial spurting, 34 with active oozing, 35 with nonbleeding visible vessel and 125 with adherent clots) with oral omeprazole 40 mg or placebo every 12 h for 5 days. Proton pump inhibitor therapy, in the absence of endoscopic therapy, was associated with significant ( $P < 0.001$ ) reductions in continued or further bleeding, need for surgery, and transfusion requirements, and a lower rate of mortality compared to placebo. (Figure 1) However, the results of this study have probably been over-interpreted; since the investigators did not use endoscopic haemostatic therapy, these findings are of very limited relevance to clinical practice in the USA or Europe.

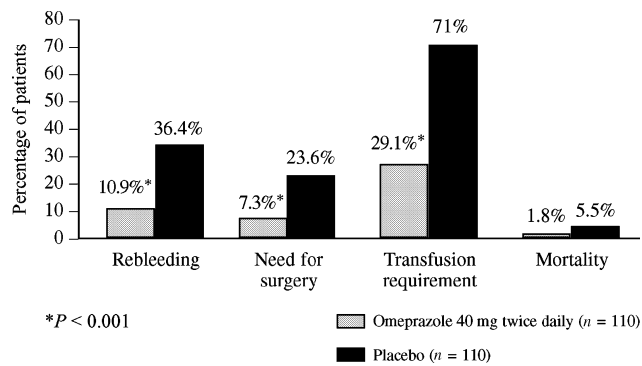


Figure 1. Oral proton pump inhibitor therapy in patients with peptic ulcer bleeding is associated with significant reductions in the incidence of re-bleeding, the need for surgery, transfusion requirements and patient mortality as compared to placebo. Figure adapted from ref. 8.

Intravenous proton pump inhibitor formulations are a further development offering the prospect of rapid and precise control of intragastric acidity, which may be critical for initial haemostasis. Despite the lack of evidence from US-based, randomized controlled clinical trials, and although they do not have approval from the US Food and Drug Administration for the management of upper GI tract bleeding in general or peptic ulcer bleeding in particular, intravenous proton pump inhibitor therapy is already widely used, based upon study results from European and Asian countries.

A double-blind, randomized, controlled trial from Hong Kong has unequivocally demonstrated the added benefit of intravenous proton pump inhibitor therapy in bleeding ulcer patients after endoscopic treatment.<sup>9</sup> Patients ( $n = 240$ ) admitted with ulcer bleeding underwent urgent endoscopy within 24 h. Following the establishment of endoscopic haemostasis, they were randomized to receive intravenous placebo or omeprazole (administered as an 80 mg IV bolus followed by an 8 mg/h infusion for 72 h). Thereafter, all patients were treated daily with 20 mg oral omeprazole for 8 weeks. The trial was terminated early when an interim analysis demonstrated significant benefits in the group treated with the intravenous proton pump inhibitor; the incidence of recurrent bleeding within 30 days was 6.7% compared to 22.5% in the placebo-treated group.

Bardou *et al.*<sup>10</sup> performed a meta-analysis of 30 randomized controlled clinical trials (a total of 3530 high risk, Forrest Ia to IIb patients) that compared the efficacy of different pharmacological treatments in patients with acute ulcer bleeding. The pharmacotherapy

was categorized into four groups: (i) high dose IV proton pump inhibitor (80 mg bolus followed by 6–8 mg/h constant infusion); (ii) all other doses and routes of proton pump inhibitor therapy except high-dose IV; (iii) H<sub>2</sub>RAs; (iv) somatostatin and octreotide in combination. Compared to placebo, all the pharmacotherapy regimens significantly decreased re-bleeding (risk difference, –12.2%; 95% CI: 16.6 to –7.8) and mortality (–1.9%, 95% CI: –2.6 to –1.2). The use of high-dose IV proton pump inhibitor therapy, most often initiated after endoscopic therapy, significantly decreased re-bleeding compared with H<sub>2</sub>RA therapy (–20.0%, 95% CI: –21.4% to –19.0%) and placebo (–15.6%, 95% CI: –16.1 to –15.1). Compared to placebo, high-dose IV proton pump inhibitor therapy was associated with a decrease in mortality (–2.8%, 95% CI: –4.5% to –1.1); proton pump inhibitor therapy (not IV high-dose) was associated with a decrease in re-bleeding (–19.7%, 95% CI: –23.4% to –15.8%) and mortality (–2.4%, 95% CI: –2.5% to –2.4%). Neither H<sub>2</sub>RA therapy nor somatostatin/octreotide had a beneficial effect on reducing re-bleeding or mortality.

Barkun *et al.*<sup>11</sup> found that high-dose oral therapy (40 mg pantoprazole twice daily for 5 days) and intravenous therapy (80 mg bolus followed by 8 mg/h for 3 days) produced equivalent rates of re-bleeding (7.3% and 5.9%) in patients with bleeding ulcers initially treated endoscopically.

#### LONG-TERM MANAGEMENT: IDENTIFICATION AND MODIFICATION OF RISK FACTORS

Cure of *Helicobacter pylori* infection is considered to be the standard treatment in those presenting with *H. pylori*-associated peptic ulcer. There is unequivocal evidence supporting *H. pylori* eradication in patients with a peptic ulcer haemorrhage: treatment of infection decreases recurrent bleeding by 17% (number needed to treat, NNT = 6) compared with acute ulcer healing treatment alone.<sup>12</sup> Treatment of *H. pylori* infection was also superior to the combination of acute ulcer healing treatment and subsequent maintenance treatment with an H<sub>2</sub>RA or omeprazole.<sup>12</sup> Because patients may be discharged from the hospital before their *H. pylori* status has been established, appropriate measures need to be taken such that these individuals are properly followed up and, if feasible, at least a noninvasive *H. pylori* test is done. Furthermore, even when tested during a hospital admission for ulcer bleeding, the testing method used

Table 1. Efficacy of diagnostic methods for *H. pylori* infection during upper gastrointestinal bleeding. Adapted from ref. 13

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Rapid urease test	48.5	100	100	22.2	55.1
<sup>13</sup> C-Urea breath test	91	77.8	96.8	53.8	89.4
Serology	89.5	80	96.8	53	88.3
Histology	86.3	100	100	53.5	88.1

may influence the accuracy of the results and there might be more false negative test results compared to the routine setting described below.

A comparison of the sensitivity and specificity of diagnostic methods was performed in 78 patients with endoscopically proven upper gastrointestinal bleeding of peptic origin.<sup>13</sup> The prevalence of *H. pylori* infection was 87.2%, which is higher than would be expected among patients presenting in the USA with complicated peptic ulcer disease. Of the four diagnostic methods evaluated, the rapid urease test had the lowest sensitivity (Table 1). The prior consumption of a proton pump inhibitor or an antibiotic resulted in a high rate of false-negative results from the rapid urease test and the urea breath test (UBT), while these agents had no effect on the performance of serology or histology. These results were confirmed in a later study by Wildner-Christensen *et al.*, who observed a decrease in the sensitivity of the rapid urease test from 96% in those with no blood present in the stomach to 60% in those with blood present ( $P = 0.006$ ). Neither the sensitivity nor the specificity of the <sup>13</sup>C-UBT was affected by the presence of blood in the stomach.<sup>14</sup>

*H. pylori* status does not appear to affect the initial rate of early re-bleeding. Lin *et al.*<sup>15</sup> enrolled 65 patients with bleeding peptic ulcer (24 with gastric ulcer, 41 with duodenal ulcer) in whom initial haemostasis had been achieved with endoscopic therapy. Following 3 days of intravenous proton pump inhibitor therapy, all patients (30 *H. pylori*-positive, 35 *H. pylori*-negative) were treated with 20 mg omeprazole once daily for 2 months. Intra-gastric pH was significantly higher in those infected with *H. pylori* compared to uninfected patients (6.54 vs. 6.05,  $P < 0.001$ ); however, no significant differences were observed in the number of re-bleeding episodes (two vs. three), volume of blood transfusion (median 1000 vs. 750 mL), or duration of hospital stay (6 vs. 7 days).

Patients requiring treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and those who use

chronic aspirin therapy, even at low cardioprotective doses, will likely benefit from co-therapy with a proton pump inhibitor to reduce their risk of re-bleeding.<sup>16–18</sup>

## CONCLUSIONS

In European countries the public health services provide access to endoscopic procedures for virtually all patients. Therefore, endoscopic interventions for the control of bleeding and risk stratification are available for most patients with acute peptic ulcer bleeding. The increasing reliance on, and success of endoscopic and pharmacological therapies has limited the opportunity for surgeons to gain experience in the surgical management of peptic ulcer bleeding.

Proton pump inhibitor therapy is more effective than treatment with an H<sub>2</sub>RA. Both intravenous and oral formulations of proton pump inhibitor therapy have been evaluated in randomized controlled trials of patients with peptic ulcer bleeding. Oral proton pump inhibitor therapy is adequate and appropriate for patients hospitalized with upper gastrointestinal tract bleeding and subsequently found at endoscopy to have an ulcer without major stigmata of recent haemorrhage. This comprises most patients hospitalized in the USA for ulcer bleeding. The use of high-dose oral or intravenous proton pump inhibitor therapy may be an appropriate treatment strategy for patients after endoscopic treatment of major stigmata in countries where there is limited access to endoscopic treatment. In the USA, only pantoprazole is currently available as an IV formulation. Intravenous lansoprazole and esomeprazole are currently in development. At this time, however, no proton pump inhibitor is specifically approved for the management of peptic ulcer bleeding.

Assessment of *H. pylori* status in all patients with peptic ulcer – and eradication therapy for infected patients – is currently accepted as a standard of care. Patients receiving aspirin or other NSAID will benefit from co-therapy with a proton pump inhibitor or

misoprostol to reduce their risks of recurrent ulcer and further ulcer bleeding.

#### REFERENCES

- 1 Higham J, Kang J-Y, Majeed A. Recent trends in admission and mortality due to peptic ulcer in England: Increased frequency of hemorrhage among older subjects. *Gut* 2002; 50: 460–4.
- 2 Laine LA. Management of ulcers with adherent clots. *Gastroenterology* 2002; 123: 632–6.
- 3 Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994; 331: 717–27.
- 4 Jensen DM, Kovacs TOG, Jutabha R, *et al.* Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. *Gastroenterology* 2002; 123: 407–13.
- 5 Cook DJ. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992; 102: 139–48.
- 6 Marmo R, Rotondano G, Bianco MA, *et al.* Outcome of endoscopic treatment for peptic ulcer bleeding: Is a second look necessary? A meta-analysis. *Gastrointest Endosc* 2003; 57: 62–7.
- 7 Gisbert JP, Gonzalez X, Calvet M, *et al.* Proton pump inhibitors versus H<sub>2</sub>-antagonists: a meta-analysis of the efficacy in treating bleeding peptic ulcer. *Aliment Pharmacol Ther* 2001; 15: 917–27.
- 8 Khuroo MS, Yattoo GN, Javid G, *et al.* A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med* 1997; 336: 1054–8.
- 9 Lau JYW, Sung JYJ, Lee KKC, *et al.* Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000; 343: 310–6.
- 10 Bardou M, Toubouti YM, Benhaberou-Brun D, *et al.* High dose intravenous proton pump inhibition decrease both re-bleeding and mortality in high-risk patients with acute peptic ulcer bleeding: a series of meta-analyses. *Gastroenterology* 2003; 124: A-625(Abstract W1079).
- 11 Barkun AN, Adam V, Kennedy W, Fallone CA, Herba K, Bardou M. The cost-effectiveness of high dose oral versus intravenous proton pump inhibition in high-risk patients with bleeding peptic ulcers having undergone therapeutic endoscopy. *Gastroenterology* 2003; 124(4): A627(Abstract M1805).
- 12 Sharma VK, Sahai AV, Corder FA, Howden CW. *Helicobacter pylori* eradication is superior to ulcer healing with or without maintenance therapy to prevent further ulcer haemorrhage. *Aliment Pharmacol Ther* 2001; 15: 1939–47.
- 13 Grino P, Pascual S, Such J, *et al.* Comparison of diagnostic methods for *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding. *Scand J Gastroenterol* 2001; 36: 1254–8.
- 14 Wildner-Christensen M, Touborg Lassen A, Lindebjerg J, Schaffalitzky de Muchadell OB. Diagnosis of *Helicobacter pylori* in bleeding peptic ulcer patients, evaluation of urea-based tests. *Digestion* 2002; 66: 9–13.
- 15 Lin H-J, Tseng G-Y, Hsieh Y-H, *et al.* Will *Helicobacter pylori* affect short-term re-bleeding in peptic ulcer bleeding patients after successful endoscopic therapy? *Am J Gastroenterol* 1999; 94: 3184–8.
- 16 Kimmey MB, Lanas A. Review article: appropriate use of proton pump inhibitors with traditional nonsteroidal anti-inflammatory drugs and COX-2 selective inhibitors. *Aliment Pharmacol Ther* 2004; 19(Suppl. 1): 60–5.
- 17 Fendrick AM, Garabedian-Ruffalo SM. A clinician's guide to the selection of NSAID therapy. *Pharm Ther* 2002; 27: 579–82.
- 18 Lai KC, Lam SK, Chum KM, *et al.* Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med* 2002; 346: 2033–8.