# ACUTE UPPER GASTROINTESTINAL HEMORRHAGE: PHARMACOLOGIC MANAGEMENT

**SUMMARY**

Non-variceal bleeding: Recurrent gastrointestinal bleeding (GIB) occurs in 15-20% of patients with upper gastrointestinal (GI) hemorrhage. Intravenous proton pump inhibitor (PPI) therapy, administered after successful endoscopic therapy, has been shown to decrease the incidence of rebleeding in high-risk patients and is preferred over $H_2$-receptor antagonists ($H_2$RA). The eradication of *Helicobacter pylori* has been shown to decrease recurrence of peptic ulcer disease as well as bleeding.

Variceal bleeding: Endoscopic therapy is first-line therapy in the management of bleeding esophageal varices. Although octreotide should not be considered a substitute, it has been successfully used to achieve hemostasis and provides an option in the circumstances where endoscopy is not immediately available or possible. Octreotide is also effective in the prevention of rebleeding following sclerotherapy or ligation and is preferred over vasopressin due to similar efficacy and fewer adverse effects. Antibiotic prophylaxis for cirrhotic inpatients with GIB is efficacious in reducing the number of deaths and bacterial infections. The choice of antibiotic should be made based on local conditions such as bacterial resistance profile and treatment cost.

**RECOMMENDATIONS**

- **Level 1**

  *Non-variceal bleeding*
  - Endoscopy should be performed within 24 hours of presentation.
  - Proton pump inhibitors (PPI) should be administered to decrease the incidence of rebleeding for up to 72 hours.
  - $H_2$-receptor antagonists ($H_2$RA) should not be used in the acute management of non-variceal gastrointestinal hemorrhage.
  - Test for and treat *Helicobacter pylori* infection.

  *Variceal bleeding:*
  - Endoscopy should be performed within 12 hours of presentation.
  - Octreotide is the drug of choice for patients with bleeding esophageal varices.
  - Prophylactic antibiotic treatment with ceftriaxone or fluoroquinolones (norfloxacin / ciprofloxacin) for not more than 7 days should be initiated for patients with cirrhosis and variceal bleeding.
- **Level 2**
  - *Non-Variceal bleeding*: Recommended Pantoprazole dosing is 40 mg IV Q12 hrs for initial therapy and transition to oral / enteral when clinically appropriate.
  - *Variceal bleeding*: Octreotide 100 mcg IV bolus x1, then 25-50 mcg/hr for 2-5 days
- **Level 3**
  - Duration of Q12 hr PPI therapy is at the clinician's discretion.

**EVIDENCE DEFINITIONS**

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

**LEVEL OF RECOMMENDATION DEFINITIONS**

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.



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## INTRODUCTION

Non-variceal bleeding:

The management of acute GI hemorrhage includes volume resuscitation (crystalloid, colloid, and blood), endoscopic therapy, and/or surgery. Unstable patients should receive a 2 liter crystalloid bolus and urinary catheter insertion for assessment of end-organ perfusion. Unfortunately, recurrent bleeding occurs in 15-20% of cases (1). Patients with endoscopic evidence of active arterial bleeding or non-bleeding visible vessel (NVBB) are at highest risk (90% and 50%, respectively) (2). Those with non-bleeding adherent clot, flat spot, or clean ulcer base have a 25%, <10%, and <5% rebleeding risk, respectively (2). The potential benefit of pharmacologically raising local pH arises from *in vitro* studies demonstrating that coagulation and platelet aggregation are pH dependent (8). Despite medical and surgical advances, the mortality associated with recurrent bleeding remains 10-14% (3). Multiple meta-analyses have demonstrated more consistent pH attainment and probably decreased rate of rebleeding associated with PPIs compared to $H_2$RAs (4,9,10). Current consensus guidelines recommend high-dose PPI therapy only due to consistently demonstrated reduction in risk of rebleeding and need for surgical intervention (11). More recently, the need for high-dose continuous infusion PPI therapy has been investigated and there was no difference in rebleeding, hospital length of stay, or mortality (12). In patients with upper GI bleed (UGIB) who require a nonsteroidal anti-inflammatory drug (NSAID), a PPI with a cyclooxygenase-2 inhibitor is the preferred combination to reduce the risk of rebleeding. Also, in patients with UGIB who require secondary cardiovascular prophylaxis, acetylsalicylic acid (ASA) should be started as soon as cardiovascular risks outweigh UGIB risks, which is usually within 7 days. ASA plus PPI therapy is preferred over clopidogrel alone to reduce rebleeding (3).

Variceal Bleeding:

Primary management of esophageal variceal bleeding is endoscopic therapy (7). However, several medications have been evaluated as adjunctive therapy to endoscopy. These agents include vasopressin, glypressin (or terlipressin), somatostatin, and octreotide. Vasopressin and octreotide are the only agents commercially available in the United States. The use of vasopressin is intended to decrease portal venous pressure and increase clotting and hemostasis. Although vasopressin may provide effective control of bleeding, there is no evidence that overall survival is improved and it has several potential adverse effects including myocardial ischemia. Octreotide, a synthetic somatostatin analogue, is more effective in achieving initial control of bleeding and also as an adjunct to endoscopic sclerotherapy to prevent rebleeding. Octreotide also has fewer complications compared to vasopressin (7,13-19).

## LITERATURE REVIEW

Non-variceal Bleeding:

Green et al. conducted an *in vitro* study demonstrating that coagulation and platelet aggregation are optimal at a local pH of 7.4. Clotting times doubled at a pH of 6.4 and quadrupled at a pH of 6. Platelet aggregation was 77% (normal 70-84%) at a pH of 7.4, but this decreased to 24% at a pH of 6.8 and no aggregation was observed at a pH of 5.9 (8). Based on this information, the goal of pharmacologic therapy is to maintain an intragastric pH ≥ 6 to facilitate adequate clotting.

The use of $H_2$RAs versus PPIs has been reviewed in a few clinical trials and a number of meta-analyses (4,9,10). Based on the currently available information, PPIs have been demonstrated to more consistently maintain an intragastric pH~6, are associated with fewer rebleeding episodes or need for surgery compared to either $H_2$RAs or placebo (3,4). In patients with actively bleeding ulcers or NBVV, PPIs have been shown to decrease mortality (3).

Current guidelines recommend high-dose continuous infusion PPIs (e.g., pantoprazole 80 mg IV bolus, then pantoprazole 8 mg/hr). However, two recent trials and two meta-analyses have demonstrated no difference in efficacy with low-dose therapy (e.g. pantoprazole 40 mg IV Q12-24 hrs) compared to the high-dose continuous infusion (12,20-23). Andriulli et al. randomized 474 patients to receive either high-dose (PPI 80 mg bolus, 8mg/hr infusion, n=238) therapy or low-dose (PPI 40 mg IV q 24 hrs, n=236). The authors demonstrated no difference in rebleeding (11.8% vs. 8.1%, p=0.18), need for surgery (1.3% vs. 0.4%, p=0.62), or mortality (0.8% both) (12). Similarly, Hus et al. randomized 120 patients to either high dose (PPI 80 mg bolus, 8 mg/hr, n=60) or low-dose (PPI 80 mg bolus, 40 mg IV Q6 hrs, n=60). The


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authors demonstrated no difference in rebleeding (6% vs. 8.3%), hospital length of stay, need for surgery or mortality (20).

Recently, Jensen et al. showed that after hemostasis has been achieved with endoscopic treatment for patients with peptic ulcer bleeding, rebleeding rates for Forrest 1B patients at 72 hours were similar with esomeprazole (5.4%) and placebo (4.9%), whereas rebleed rates for all other major stigmata of recent hemorrhage (Forrest 1A, 2A, 2B) were lower for PPI than placebo. This showed that treatment with PPI for Forrest 1B patients needed to be re-evaluated (21).

**Forrest Classification for GIB**

| Class | Definition | Re-bleeding rate (%) |
|---|---|---|
| 1A | Spurting arterial vessel | 80-90 |
| 1B | Oozing hemorrhage | 10-30 |
| 2A | Non-bleeding vessel | 50-60 |
| 2B | Adherent clot | 25-35 |
| 2C | Ulcer base with black spot sign | 0-8 |
| 3 | Clean base | 0-12 |

The treatment of patients who are demonstrated to have *Helicobacter pylori* infection has been demonstrated to decrease rebleeding rates and facilitate ulcer healing. Jaspersen et al. evaluated 51 patients with bleeding duodenal ulcers, who were biopsy-proven *H. pylori* positive. Patients were randomized to receive 40 mg omeprazole each day with ampicillin 1 gm twice daily in the treatment group versus omeprazole alone in the control group. Eradication of *H. pylori* was evaluated at repeat endoscopy, both histologically and by urease testing. Ulcer recurrence was reduced in the treatment group to 10% versus 41% in the control group ($p<0.05$). Rebleeding was also significantly reduced to 0% in the treatment group compared to 27% in the control group ($p<0.01$) (5).

In summary, PPI are the preferred agents for the treatment of non-variceal GI bleeds. As there appears to be no difference in outcome, it is recommended that a once- or twice-daily PPI regimen be used instead of a high-dose continuous infusion. Patients who are confirmed positive for *H. pylori* should be treated with appropriate antimicrobial agents in addition to their PPI therapy. Also, in patients with liver cirrhosis that have variceal bleeding, prophylactic antibiotics with norfloxacin/ciprofloxacin or ceftriaxone has been shown to decrease mortality.

Variceal Bleeding:
Management of bleeding esophageal varices remains primarily endoscopic with the medications playing an adjunctive role in an effort to decrease rebleeding and improve survival. There are a number of agents which have been studied including vasopressin, glypressin (or terlipressin), somatostatin, and octreotide. Only vasopressin and octreotide are available in the United States (7,13-19). Two controversies exist within the literature: 1) octreotide versus vasopressin and 2) octreotide alone compared with octreotide plus endoscopic therapy.

Several studies have been conducted comparing vasopressin to octreotide. Hwang et al. compared in a randomized, controlled trial, the safety and efficacy of vasopressin and octreotide in the treatment of 48 cirrhotic patients with acute variceal hemorrhage (no mention of endoscopic intervention during treatment) (13). Patients were randomized to receive a continuous infusion of either octreotide (100 mcg bolus followed by 25 mcg/hr infusion) or vasopressin (0.4 units/minute infusion) for 24 hours. Initial control of bleeding was achieved in 88% of the octreotide patients versus 54% of the vasopressin patients ($p=0.03$). There was no significant difference in rebleeding at 24 hours. Vasopressin was associated with more adverse effects (including headache, chest pain, and abdominal pain) than octreotide (46% versus 13%, $p=0.02$) (13). Corley et al. performed a meta-analysis of all trials comparing octreotide versus vasopressin or terlispressin. Octreotide was found to have a significant benefit over vasopressin or terlipressin in preventing rebleeding (RR 0.58; 95% CI 0.42-0.81) (15).


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Three studies have been conducted evaluating initial bleeding control with octreotide alone, endoscopic sclerotherapy alone or the combination. Jenkins et al. conducted a multicenter, open-label, randomized trial comparing octreotide with endoscopic sclerotherapy (ES) in 150 patients with acute variceal hemorrhage. Octreotide was administered as a continuous infusion (50 mcg/hr) for 48 hours. All patients in the octreotide group received ES at the end of the 48-hour infusion. There was no significant difference in bleeding control at 48 hours between the ES only group and the octreotide group (82% versus 85%) (16). Similarly, Besson et al. conducted a multicenter, prospective, double-blind, randomized trial to compare ES alone with ES plus octreotide (25 mcg/hr for 5 days) in 199 patients with cirrhosis and acute variceal bleeding. For the primary endpoint of survival without rebleeding at 5 days, the combination of ES plus octreotide was more effective than ES alone (87% versus 71%, p=0.009) (17). Finally, Freitas et al. conducted a prospective, randomized trial comparing octreotide alone versus ES for the prevention of early rebleeding in patients with recent bleeding from esophageal varices. They also compared ES alone with ES plus octreotide in patients with actively bleeding esophageal varices. Octreotide was administered as a continuous infusion (25 mcg/hr for 48 hours). In patients with recent bleeding, there was no significant difference in hemostasis between ES and octreotide at 48 hours. In patients with active bleeding, ES plus octreotide was superior to ES alone in achieving initial hemostasis (98% vs. 74%, p<0.001). The difference remained significant at 48 hours (81% vs. 60%, p < 0.04) (18).

Chavez-Tapia et al. evaluated twelve trials (1241 patients) comparing antibiotic prophylaxis with placebo or no antibiotic prophylaxis. Antibiotic prophylaxis compared with no intervention or placebo showed beneficial effects on mortality (RR 0.79, 95% CI 0.63 to 0.98), mortality from bacterial infections (RR 0.43, 95% CI 0.19 to 0.97), bacterial infections (RR 0.36, 95% CI 0.27 to 0.49), rebleeding (RR 0.53, 95% CI 0.38 to 0.74), days of hospitalization (MD -1.91, 95% CI -3.80 to -0.02), bacteremia (RR 0.25, 95% CI 0.15 to 0.40), pneumonia (RR 0.45, 95% CI 0.27 to 0.75), spontaneous bacterial peritonitis (RR 0.29, 95% CI 0.15 to 0.57), and urinary tract infections (RR 0.23, 95% CI 0.12 to 0.41) (24)

In summary, endoscopic therapy remains the most effective modality for managing variceal hemorrhage. However, the addition of octreotide at 25-50 mcg/hr appears to further improve rates of early rebleeding and is well tolerated. Vasopressin should not be used due to its significant side effect profile. There is little evidence that any of the treatment modalities have any significant impact on overall mortality.

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