

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

## ACUTE GASTROINTESTINAL HEMORRHAGE: PHARMACOLOGIC MANAGEMENT

**THESE GUIDELINES DO NOT APPLY TO STRESS ULCER PROPHYLAXIS.  
PLEASE REFER TO THE STRESS ULCER PROPHYLAXIS GUIDELINES.**

### SUMMARY

**Non-variceal Bleeding:** Recurrent gastrointestinal bleeding occurs in 15-20% of patients with upper gastrointestinal hemorrhage. Maintaining a local pH > 5.9 is necessary for coagulation and platelet aggregation. Intravenous omeprazole, administered after successful endoscopic therapy, has been shown to decrease rebleeding in high-risk patients. Three randomized controlled trials comparing high dose bolus followed by continuous infusion of proton pump inhibitors versus H<sub>2</sub> blockers and placebo have shown a decreased incidence of rebleeding and need for surgical intervention (9,19,20). The eradication of *Helicobacter pylori* has been shown to decrease recurrence of peptic ulcer disease as well as the recurrence of bleeding (21,22).

**Variceal Bleeding:** Endoscopic therapy is considered to be 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 circumstances where endoscopy is not immediately available or possible. Octreotide is also effective in the prevention of rebleeding following sclerotherapy or ligation. Vasopressin should be avoided as octreotide is at least as effective and is associated with fewer complications.

### RECOMMENDATIONS

- **Level 1**
  - **High doses proton pump inhibitors should be administered to decrease the incidence of non-variceal gastrointestinal rebleeding.**
  - **Continuous H<sub>2</sub> receptor antagonist infusions are not effective in the acute management of non-variceal gastrointestinal hemorrhage.**
  - **Both H<sub>2</sub> receptor antagonists and proton-pump inhibitors may be used to promote ulcer healing.**
  - **Test for and treat *Helicobacter pylori* infection.**
  - **Octreotide (25-50mcg/hr for 2-5 days), used in conjunction with endoscopic therapy, is the drug of choice for patients with bleeding esophageal varices.**
- **Level 2**
  - **None**
- **Level 3**
  - **None**

### 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.

## **INTRODUCTION**

### Non-variceal Bleeding

The acute management of gastrointestinal (GI) hemorrhage includes volume resuscitation, endoscopic therapy, and/or surgery. Unfortunately, recurrent bleeding occurs in 15-20% of cases (1). Patients with endoscopic evidence of active arterial bleeding or a non-bleeding visible vessel are at highest risk (90% and 50%, respectively) (2). Those with a non-bleeding adherent clot, flat spot, or clean ulcer base have a 25%, <10%, and <5% rebleeding risk, respectively (2). Despite medical and surgical advances, the mortality associated with recurrent bleeding remains significant. This has led investigators to evaluate the efficacy of adjunctive therapy with H<sub>2</sub> receptor antagonists and proton pump inhibitors. The potential benefit of pharmacologically raising local pH arises from in-vitro studies demonstrating that coagulation and platelet aggregation are pH dependent (3). H<sub>2</sub> receptor antagonists have not demonstrated a consistent benefit (4). They are associated with the development of tolerance and subsequent loss of pH control (5,6). Initial studies evaluating proton pump inhibitors have yielded conflicting results (7,8). This is likely related to differences in dosing regimens, inclusion criteria, and endoscopic practices. More recent studies, have demonstrated a consistent reduction in risk of recurrent bleeding and need for surgical intervention (9).

### Variceal Bleeding

Several drugs have been evaluated for the management of acute variceal hemorrhage, including 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 it may provide effective control of bleeding, there is no evidence that overall survival is improved. The potential development of vasoconstrictive adverse effects, including myocardial ischemia, is an important disadvantage to the use of vasopressin. Studies evaluating vasopressin/terlipressin often excluded patients at highest risk for complications from the vasoactive effects of these agents. Several clinical trials have demonstrated that octreotide is more effective and has fewer complications than vasopressin (10-12). Octreotide, a synthetic analogue of somatostatin, has been compared to endoscopic therapy for initial control of bleeding and also evaluated as an adjunct to endoscopic sclerotherapy to prevent rebleeding (12-16).

## **LITERATURE REVIEW**

### Non-variceal Bleeding

Green and colleagues conducted an in-vitro study demonstrating that coagulation and platelet aggregation are optimal at a local pH of 7.4 (2). 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. Twenty-four percent aggregation occurred at a pH of 6.8 and no aggregation was noted at a pH of 5.9.

Walt and colleagues performed a multi-center, randomized, placebo-controlled trial to evaluate the efficacy of famotidine in patients with upper GI bleeding from gastric or duodenal ulcers (4). Famotidine was administered as a 10mg bolus followed by a continuous infusion of 3.2 mg/hr for 72 hours. After the 72 hour infusion, all patients received famotidine 40 mg/day to promote ulcer healing. Endoscopic therapy was not used. The primary endpoint was death from any cause prior to hospital discharge. Secondary endpoints included rebleeding and surgery. One thousand five hundred patients were evaluated. There was no significant difference in mortality between the famotidine and placebo groups [6.2% versus 5%, OR 1.37 (95% CI 0.77-2.44)]. There was also no significant difference in the incidence of rebleeding or need for surgery.

Lau and colleagues performed a randomized, double-blind, placebo-controlled trial to evaluate the effect of high-dose omeprazole on recurrent bleeding within 30 days after endoscopy (9). Patients with actively bleeding ulcers or ulcers with non-bleeding visible vessels, who were successfully treated with endoscopy, were eligible. Patients were excluded if endoscopy was unsuccessful or ulcers with clean bases/flat pigments were identified. Patients were randomized to either placebo or omeprazole (80mg bolus followed by 8 mg/hr for 72 hours). Upon completion of the infusion, all patients received omeprazole 20mg/day orally for 8 weeks. Two hundred forty patients were included in the analysis. Bleeding recurred in 6.7% (8/120) of omeprazole patients compared to 22.5% (27/120) of placebo patients (p<0.001). Most episodes occurred within 3 days for both groups. Secondary analyses revealed

a significantly shorter length of hospitalization and lower number of blood transfusions in the omeprazole group. There was no difference in 30-day mortality or ulcer healing at 8 weeks.

Hasselgren and colleagues also compared omeprazole infusion versus placebo following endoscopic treatment of bleeding ulcers, Forrest classification Ia, Ib, IIa, and IIb (20). This was a multicenter, randomized, double blinded, placebo controlled trial which enrolled 322 patients in Sweden. 159 patients received omeprazole, while 163 received placebo. The need for surgery was reduced in the omeprazole group 2.5% (4/159) compared to the control group 9% (16/163), ( $p < 0.003$ ). They also found that in those patients that severity of continued bleeding was less in the treatment group.

Brunner and colleagues evaluated the effect of four pantoprazole regimens on gastric pH in healthy volunteers (17). An 80mg bolus (over 2 minutes) followed by 8 mg/hr achieved and maintained a pH  $> 6$  in 84% of patients. The desired pH was reached within 20 minutes.

Jaspersen and colleagues evaluated 51 patients with bleeding duodenal ulcers, who were biopsy proven H pylori positive (21). Patients were randomized to receive 40 mg omeprazole each day with 1 gm amoxicillin twice a day 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 10% (3/29) versus 41% (9/22) in the control group ( $p < 0.05$ ). Rebleeding also was significantly reduced in the treatment group 0% (0/29) compared to 27% (6/22) in the control group ( $p < 0.01$ ).

#### Variceal Bleeding

In a randomized, controlled trial, Hwang and colleagues compared the safety and efficacy of vasopressin and octreotide in the treatment of 48 cirrhotic patients with acute variceal hemorrhage (10). Patients were randomized to receive a continuous infusion of either octreotide (100mcg bolus followed by 25mcg/hr) or vasopressin (0.4U/min) for 24 hours. Initial control of bleeding was achieved in 88% of octreotide patients versus 54% of vasopressin patients ( $p = 0.03$ ). There was no significant difference in recurrent bleeding at 24 hours. Vasopressin was associated with more adverse effects (including headache, chest pain, and abdominal pain) than octreotide (46% versus 13%,  $p = 0.02$ ). A meta-analysis of existing trials comparing octreotide versus alternative interventions was recently performed by Corley and colleagues (12). Octreotide was found to have a significant benefit over vasopressin/terlipressin in preventing rebleeding (RR 0.58; 95% CI 0.42-0.81).

In a multicenter, open-label, randomized trial, Jenkins and colleagues compared octreotide with injection sclerotherapy in 150 patients with acute variceal hemorrhage (13). Octreotide was administered as a continuous infusion (50mcg/hr) for 48 hours. All patients in the octreotide group received sclerotherapy at the end of the 48-hour infusion. There was no significant difference in bleeding control at 48 hours between the sclerotherapy and octreotide groups (82% versus 85%). Balloon tamponade was needed to control rebleeding in both groups.

Besson and colleagues conducted a multicenter, prospective, double-blind, randomized trial to compare sclerotherapy alone with sclerotherapy and octreotide (25mcg/hr for 5 days) in 199 patients with cirrhosis and acute variceal bleeding (14). For the primary endpoint of survival without rebleeding at 5 days, octreotide was more effective than placebo (87% versus 71%,  $p = 0.009$ ).

Freitas and colleagues conducted a prospective, randomized trial to compare octreotide alone versus endoscopic sclerotherapy (ES) for the prevention of early rebleeding in patients with recent bleeding from esophageal varices (15). They also compared ES alone with ES plus adjunctive octreotide in patients with actively bleeding esophageal varices. Octreotide was administered as a continuous infusion (25mcg/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% versus 74%,  $p < 0.001$ ). The difference remained statistically significant at 48 hours (81% versus 60%,  $p < 0.04$ ).

Octreotide has been evaluated as adjunctive therapy to endoscopic ligation and found to significantly decrease rebleeding (16).

For a review of additional literature addressing octreotide for acute variceal bleeding, refer to the article by Erstad (18).

## REFERENCES

1. Savides TJ, Jensen DM. Severe gastrointestinal hemorrhage. In: Grenvik A, Ayres SM, Holbrook PR, Shoemaker WC (Eds). Textbook of critical care. Fourth Edition. Philadelphia, WB Saunders Company, 2000, pp 1609-1616.
2. Freeman ML. The current endoscopic diagnosis and intensive care unit management of severe ulcer and other nonvariceal upper gastrointestinal hemorrhage. *Gastrointest Endosc Clin North Am* 1991; 1:209-239.
3. Green FW, Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin of blood coagulation and platelet aggregation. *Gastroenterology* 1978; 74:38-43.
4. Walt RP, Cottrell J, Mann SG, Freemantle NP, Langman MJS. Continuous intravenous famotidine for haemorrhage from peptic ulcer. *Lancet* 1992; 340:1058-1062.
5. Netzer P, Gaia C, Sandoz M, Huluk T, Gut A, Halter F, et al. Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. *Am J Gastroenterol* 1999; 94:351-357.
6. Labenz J, Peitz U, Leusing C, Tillenburg B, Blum AL, Borsch G. Efficacy of primed infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: a randomised controlled study. *Gut* 1997; 40:36-41.
7. Daneshmend TK, Hawkey CJ, Langman MJ, Logan RF, Long RG, Walt RP. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. *BMJ* 1992; 304:143-147.
8. Khuroo MS, Yattoo GN, Javid G, Khan BA, Shah AA, Gulzar GM, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med* 1997; 336:1054-1058.
9. Lau JY, Sung JJ, Lee KK, Yung M, Wong SK, Wu JC, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000; 343:310-316.
10. Hwang SJ, Lin HC, Chang CF, Lee FY, Lu CW, Hsia HC, et al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol* 1992; 16:320-325.
11. Avgerinos A, Armonis A, Raptis S. Somatostatin and octreotide in the management of acute variceal hemorrhage. *Hepato-Gastroenterol* 1995;42: 145-150.
12. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology* 2001;120: 946-954.
13. Jenkins SA, Shields R, Davies M, Elias E, Turnbull AJ, Bassendine MF, et al. A multicentre randomized trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997; 41:526-533.
14. Besson I, Ingrand P, Person B, Boutroux D, Heresbach D, Bernard P, et al. Sclerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med* 1995; 333:555-560.
15. Freitas DS, Sofia C, Pontes JM, Gregorio C, Cabral JP, Andrade P, et al. Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepato-Gastroenterol* 2000; 47:1310-1314.
16. Sung JJ, Chung SCS, Yung MY, Lai CW, Lau JYW, Lee YT, et al. Prospective randomized study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995; 346:1666-1669.
17. Brunner G, Luna P, Hartmann M, Wurst W. Optimizing the intragastric pH as a supportive therapy in upper GI bleeding. *Yale J Biol Med* 1996; 69:225-231.
18. Erstad BL. Octreotide for acute variceal bleeding. *Ann Pharmacother* 2001; 35:618-626.
19. Goletti O, Sidoti F, Lippolis PV, De Negri F, Cavina E. Omeprazole versus ranitidine plus somatostatin in the treatment of severe gastroduodenal bleeding: a prospective, randomized, controlled trial. *Ital J Gastroenterol* 1994; 26:72-74.

20. Hasselgren G, Lind T, Lundell L, Aadland E, Efskind P, Falk A, Hyltander A, Soderlund C, Eriksson S, Fernstrom P. Continuous Intravenous Infusion of Omeprazole in Elderly Patients with Peptic Ulcer Bleeding. *Scand J Gastroenterol* 1997; 32:328-333.
21. Jaspersen D, Koerner T, Schorr W, Brennenstuhl M, Raschka C, Hammar C. Helicobacter pylori eradication reduces the rate of rebleeding in ulcer hemorrhage. *Gastrointest Endosc* 1995; 41:5-7.
22. Rokkas T, Karameris A, Mavrogeorgis A, Rallis E, Giannikos N. Eradication of Helicobacter pylori reduces the possibility of rebleeding in peptic ulcer disease. *Gastrointest Endosc* 1995; 41:1-4.