Acute upper gastrointestinal bleeding in critically ill patients: Causes and treatment modalities

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Upper gastrointestinal bleeding from peptic ulcers or other nonvariceal causes generally stops spontaneously; if it fails to do so, aggressive management is required. Such measures also are necessary for patients at high risk for rebleeding. Endoscopic therapy achieves hemostasis in >90% of bleeding patients and reduces mortality. After successful hemostasis of the initial bleeding episode, the primary concern becomes the prevention of rebleeding, which occurs in up to 20% of patients. Acid suppression with histamine-2–receptor antagonists has been widely used for many years to prevent recurrent bleeding. However, in acutely bleeding patients, these agents have not been shown to reduce the number of episodes of further bleeding or rebleeding or to reduce the need for transfusions or surgery. Omeprazole, an intravenous proton pump inhibitor, significantly reduced the rate of rebleeding in a recent placebo-controlled trial in which only patients with endoscopic confirmation of successful hemostasis were enrolled. Although this drug does not seem to reduce the need for surgical intervention or to decrease mortality, the trial does indicate the promise of intravenous proton pump inhibitors in reducing upper gastrointestinal bleeding. Evidence from additional well-controlled trials is needed to confirm this finding. The use of proton pump inhibitors in this setting also may have a positive economic impact, and a decrease in the percentage of patients who experience rebleeding will eliminate the cost of further management strategies in those cases. (Crit Care Med 2002; 30[Suppl.]:S365–S368)

KEY WORDS: peptic ulcer rebleeding; upper gastrointestinal bleeding; *Helicobacter pylori*; prophylaxis; treatment; endoscopy; hemostasis; intravenous; proton pump inhibitors; pantoprazole; histamine-2–receptor antagonists; cost of therapy

Acute upper gastrointestinal bleeding is a common problem in critical care medicine. In the United States, it accounts for approximately 300,000 admissions to the hospital each year (1, 2). Optimal therapeutic management requires careful determination both of the bleeding's sources and its characteristics. The various treatment options include endoscopic interventional techniques and antisecretory therapy. Acid suppressives such as histamine-2–receptor antagonists (H_2RAs) have been widely used in such patients for many years without evidence of efficacy. The superior acid suppression offered by proton pump inhibitors (PPIs) suggests that they will be more effective than H_2RAs in controlling acute bleeding in a critical care setting.

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MORTALITY, SOURCES OF BLEEDING, AND COMPLICATING CONDITIONS

The mortality rate for patients with acute upper gastrointestinal bleeding has remained relatively stable over the past 40 yrs; it ranges from 6% to 10% (3–5). These percentages may be misleading and should be lower because of significant improvements in management techniques and in transfusion practices. However, such improvements apparently are offset by the increasing number of older patients with additional complications or with other co-morbid conditions and by a more widespread use of nonsteroidal anti-inflammatory drugs (1, 2, 6).

Major causes of upper gastrointestinal bleeding in critically ill patients include variceal and acid-related sources. Variceal sources originate from the distal esophagus or the proximal gastric regions. Acid-related sources include peptic ulcer disease and stress-related mucosal damage. Other less common conditions responsible for upper gastrointestinal bleeding are Mallory-Weiss syndrome and vascular lesions. In the past 20 yrs, the distribution of sources of such bleeding has changed little. Endoscopic surveys of large numbers of patients have revealed that up to 75% of upper gastrointestinal bleeding results from acid peptic disease. Gastritis, gastric ulcer, and duodenal ulcer occur in approximately equal numbers (3, 7). Varices, esophagitis, duodenitis, and Mallory-Weiss syndrome each account for 5% to 15% of the remaining cases.

Complicating conditions include coagulopathy and splanchnic ischemia. Hemostatic disorders such as platelet disorders and disorders of coagulation factors present considerable problems. Although the role of splanchnic ischemia is not well defined, a consensus exists that mucosal hypoperfusion may play an integral part in the pathogenesis of some of these lesions, particularly in the case of reperfusion injury that occurs after the state of shock (8, 9).

GENERAL MANAGEMENT APPROACHES TO ACUTE BLEEDING

Bleeding stops spontaneously in most patients (10), but aggressive management is required when bleeding does not quickly resolve or when patients are at high risk for rebleeding. Management

priorities include the maintenance of hemodynamic function and the prevention of complications such as pulmonary aspiration (1). The initial steps in managing patients with upper gastrointestinal bleeding are shown in Table 1. Strategies include protection of the airway during massive bleeding, restoration of circulating blood volume, and correction of comorbid conditions (e.g., coagulopathy).

The threshold for intubation is low, especially because many bleeding patients are difficult to sedate and their airway management presents a challenge. The cornerstone of treating patients with hypovolemic states is the use of crystalloids and colloids to restore the circulating blood volume. Red cell transfusion may be employed to maintain the hematocrit, but other than in patients with very low hemoglobin levels, the benefits of this procedure are largely unproven (1). Co-morbid conditions such as hemostatic disorders should be treated. It is important to correct thrombocytopenia or coagulopathy with platelets or fresh-frozen plasma (1).

The development of endoscopic techniques has reduced markedly the need for surgery in patients with bleeding peptic ulcers. Once the initial bleeding episode has been controlled with hemostasis, the primary focus becomes the prevention of rebleeding, experienced by up to 20% of patients (11). The failure of endoscopic therapy coupled with continued rebleeding, especially if additional transfusions are required for hemodynamic instability, often indicates the need for interventional radiology or, more traditionally, surgical therapy.

Role of Endoscopy in Control of Acute Bleeding

Several stigmata of recent bleeding have been identified that are viewed endoscopically and can guide endoscopic therapy. The following stigmata generally are indications of the need for endoscopy: an actively bleeding ulcer, which has a rate of rebleeding of approximately 90% to 100%; a nonbleeding visible vessel, which has a rate of rebleeding of approximately 40% to 50%; and an adherent clot at the base of the ulcer (even if it is not currently bleeding), which has a rate of rebleeding between 20% and 30% (5). When there are no visible vessels, no adherent clot, and no active bleeding, the rate of rebleeding is much lower.

The main endoscopic techniques for managing bleeding are injection therapy and thermocoagulation. Employed as the sole therapy in the past, injection therapy now is the first approach in attempting to control the initial bleeding, but it works best when followed by thermocoagulation. Although sclerosing agents have been used for injection, the most commonly used injection is an epinephrine-containing solution when combination with thermocoagulation is planned (12). The two most frequently employed types of thermocoagulation are the heater probe and the bipolar coagulation probe (1, 12). Both devices deliver energy at a predetermined rate and are easily inserted through the endoscope. They allow pressure on the region to coapt the blood vessel and to reduce bleeding during the application of energy.

Endoscopic therapy is effective in achieving hemostasis in more that 90% of cases (13). The bipolar electrode and the heater probe yield comparable results with regard to hemostasis, transfusion requirements, length of hospital stay, and mortality rates (4). A meta-analysis of a large number of studies has demonstrated that endoscopic intervention decreases rates of mortality (14).

Possible Role of *Helicobacter pylori* in Acute Upper Gastrointestinal Bleeding

Endoscopy also allows assessment of the presence of *H. pylori*. This bacterium is a major causal factor of chronic type B gastritis and of duodenal ulcer (15). A study by Jaspersen et al. (15) demonstrated that the eradication of *H. pylori* significantly reduced the rates of ulcer recurrence and of rebleeding in patients with duodenal ulcers. Two published studies evaluated the possible role of this organism in acute upper gastrointestinal bleeding. The stronger of these two studies was a prospective, single center, cohort study that compared the prevalence of *H. pylori* infection in 26 critically ill patients with upper gastrointestinal bleeding after cardiac surgery to that in 229 patients with no evidence of gastrointestinal hemorrhage for up to 6 wks after cardiac surgery (16). This study showed that *H. pylori* was not associated with gastrointestinal bleeding in critically ill patients, whereas, as expected, mechanical ventilation was (16).

The second study was a retrospective analysis of data collected from a prospective, multicenter, randomized trial designed to evaluate the effectiveness of intravenous immunoglobulin in preventing infections acquired in the ICU (17). The study's subjects were 874 patients without a preexisting gastrointestinal condition. Data from logistic regression analysis show that there was a positive correlation between the presence of *H. pylori*, defined as a serum *H. pylori* immunoglobulin A antibody level of >1, and gastrointestinal bleeding (17). No such correlation was demonstrated for immunoglobulin G. Other factors associated with an increased risk of bleeding were acute hepatic failure, prolonged duration of nasogastric tube placement, and alcoholism. The value of this second study has been questioned because the measurement of immunoglobulin A antibodies against *H. pylori* antigen is a much less sensitive serological test than the measurement of immunoglobulin G antibodies (16).

Table 1. Initial steps in the management of upper gastrointestinal bleeding

Airway protection
Airway monitoring
Endotracheal intubation (if indicated)
Hemodynamic stabilization
Large bore intravenous access
Intravenous fluids
Red cell transfusion (for symptomatic anemia)
Fresh-frozen plasma, platelets (if indicated)
Consider erythropoeitin
Nasogastric oral administration
Large bore orogastric tube/lavage
Clinical and laboratory monitoring
Serial vital signs
Serial hemograms, coagulation profiles, and chemistries (as clinically indicated)
Electrocardiographic monitoring
Hemodynamic monitoring (if indicated in high-risk patients)
Endoscopic examination and therapy

Role of Acid Suppression in Control of Acute Upper Gastrointestinal Bleeding

H_2RAs. Gastric acid–suppressing agents such as H_2RAs have long been available as treatment options. The first H_2RA, cimetidine, was marketed in 1977. The success of H_2RAs in the treatment of symptomatic peptic ulcer disease was the rationale for their widespread use for the prevention of recurrent bleeding once the initial bleeding episode had been controlled with endoscopy (18). However, there is little data to support this benefit. In acutely bleeding patients, these agents have not been shown to reduce the number of transfusions, episodes of further bleeding or rebleeding, or the need for surgery (18–20).

The only report that provided evidence that intravenous H_2RAs in fact may control bleeding in such patients is a meta-analysis examining the data of 27 randomized trials in which >2500 patients were treated with H_2RAs (21). The benefits of H_2RAs to prevent rebleeding after successful endoscopy in this study are unclear because endoscopic data were not included. The results of this study suggest that H_2RAs offered a clinical benefit in patients with bleeding gastric ulcer; in such patients, they produced a decrease in the rate of continued bleeding, need for surgery, and mortality rate (21). In this trial, however, the H_2RAs had no benefit for bleeding duodenal ulcer. The findings of this meta-analysis were not confirmed by Walt et al. (20) in a large-scale, multicenter trial that compared the effects of continuous infusion of intravenous famotidine to placebo in 1005 patients hospitalized with bleeding peptic ulcer. All patients had endoscopic signs of recent hemorrhage. The H_2RA offered no benefits when compared with the placebo; the rates of rebleeding, the need for surgery, and the mortality rates in the two groups are comparable (20).

PPIs. During the past 20 yrs, PPIs have been widely used to suppress gastric acid secretion in patients with a variety of acid-related disorders (18). The efficacy of PPIs in the management of acute bleeding has been evaluated in a number of studies (22–25). Two randomized, double-blind, placebo-controlled studies yielded conflicting results (22, 23). Endoscopic hemostasis either was not used uniformly (22) or was not used at all (24). In the study by Daneshmend et al. (22), a regimen of intravenous and oral omeprazole was compared with placebo in 1147 bleeding patients with endoscopically identified upper gastrointestinal lesions. An 80-mg dose of intravenous omeprazole was administered initially, followed by three 40-mg doses given at 12-hr intervals, and then six 40-mg oral doses administered 12 hrs apart over a 3-day period. The results show that omeprazole did not reduce rebleeding, the need for transfusion or surgery, or mortality rates. These data were subject to criticism because therapeutic endoscopy was not applied uniformly and because the patient population was not restricted to those with recent episodes of bleeding or those suspected of being at high risk for rebleeding. In contrast to the findings of this study, the results of the study by Khuroo et al. (23) suggest that omeprazole was beneficial to patients with bleeding peptic ulcer or recent bleeding. These investigators (23) evaluated the efficacy of oral omeprazole in a randomized, double-blind, placebo-controlled trial involving 220 patients who had not received endoscopic therapy. Recent bleeding was determined by endoscopic diagnosis or confirmation. Oral doses of omeprazole, 40 mg, and the placebo were given twice daily for 5 days. In patients who had a nonbleeding visible vessel or an adhering clot—two of the high-risk lesions for rebleeding—omeprazole produced a dramatic reduction in recurrent bleeding and decreased the need for surgical therapy and blood transfusion. This study, too, was criticized because only diagnostic endoscopy was performed, whereas hemostatic intervention now is considered the standard of care (2, 13, 14).

The use of intravenous PPIs in patients with acute bleeding produced improvements in clinical outcomes in two randomized, double-blind, placebo-controlled studies (24, 25). In the first study, a bolus infusion of 80 mg of omeprazole was followed by continuous infusion with 8 mg/hr for 72 hrs and a 20-mg oral dose for 18 days (24). In patients who had evidence of endoscopic intervention and control of bleeding, fewer blood transfusions were required, and the amount of bleeding and the need for additional endoscopy or surgical intervention were also reduced. Mortality was not changed. The rate of recurrent bleeding was not reported. In a more recent study, Lau et al. (25) compared the efficacy of intravenous omeprazole against a placebo in preventing endoscopically confirmed rebleeding in 240 patients with upper gastrointestinal bleeding within 7 days of successful endoscopic hemostasis. All study subjects received either a placebo or 80 mg of omeprazole, given as an intravenous bolus dose, followed by an infusion of 8 mg/hr for 72 hrs, and then 20 mg/day of oral omeprazole for 8 wks. The results show that omeprazole reduced recurrent bleeding but did not affect the need for surgical intervention or decrease mortality. This well-controlled trial shows the promise of intravenous PPIs to reduce upper gastrointestinal bleeding.

Economic Considerations in Choice of Therapy for Acute Upper Gastrointestinal Bleeding

The use of PPIs in critically ill patients at risk of acute gastrointestinal bleeding has been questioned because of their higher cost as compared with intravenous H_2RAs. However, data are available suggesting that the reduction in the rate of rebleeding produced by intravenous PPIs has a positive economic impact. The cost of managing upper gastrointestinal bleeding was examined in a prospective study conducted in 1995 by Heyland et al. (26) involving 2252 patients in intensive care units in Canada, 33 of whom had significant gastrointestinal bleeding. In this study, extra costs were associated with failure to control bleeding; the treatment strategies responsible for these extra costs are shown in Table 2. At the time of this study, it was estimated that each case of upper gastrointestinal bleeding costs approximately $12,000 (Canadian). A conservative estimate of the cost of a clinically important episode of bleeding in American dollars is approximately $8000 (27). This shows how expensive nontreatment can be. Theoretically, with this estimate applied to 1000 patients and an absolute rate of rebleeding reduction assumed to be approximately 10%, the cost savings would be about $8000 per episode, or $800,000 in total. However, this assumption is based strictly on eco-

Table 2. Sources of extra costs in the intensive care unit (ICU) associated with failure to prevent rebleeding

6.6 additional hematology tests
10.8 units of blood products
23.6 days of anti-ulcer medication
11.4 more days in ICU for surviving patients
Increased number of endoscopies and surgeries

Adapted with permission from Heyland et al (26).

Aggressive antisecretory treatment with intravenous proton pump inhibitors may now be considered the standard of care for patients with a bleeding ulcer, particularly for those with an adherent clot or a nonbleeding visible vessel.

nomic information and does not include nonmonetary costs such as additional morbidity for patients. The results of a second study (28) with similar methodology as that of Heyland et al. (26) show cost benefits of using an intravenous PPI to prevent rebleeding after successful endoscopic hemostasis in patients in the ICU with upper gastrointestinal bleeding from peptic ulcer. The data were presented in an abstract at the annual meeting of the American College of Gastroenterology in 2001. This study model assumed that use of an intravenous PPI after hemostasis provided an improved patient outcome (25, 29). The results of this analysis show that incorporating intravenous PPI therapy reduced the costs associated with surgical management and other treatment strategies that were needed to deal with the additional number of bleeds that occurred in the patients who received endoscopic therapy alone. The data from these two studies (26, 28) suggest that the higher initial costs of the PPI could be offset by the subsequent reduction in rebleeding episodes requiring intervention.

CONCLUSION

Acute gastrointestinal bleeding from peptic ulcer or other nonvariceal causes is a common problem in a critical care setting, presenting a major challenge to ICU personnel. Early endoscopic intervention of select high-risk lesions is the standard of care in managing patients with such acute bleeding. The prevention of rebleeding after successful endoscopic hemostasis is critical. H_2RAs, although widely used, have not demonstrated efficacy in the prevention of rebleeding. Evidence is emerging that PPIs can reduce rebleeding episodes. Unlike intravenous H_2RAs, PPIs delivered by this route can raise and maintain intragastric pH near neutrality and also allow the formation of stable clots. Aggressive antisecretory treatment with intravenous PPIs may now be considered the standard of care for patients with a bleeding ulcer, particularly for those with an adherent clot or a nonbleeding visible vessel. In cases in which endoscopy is unavailable, risky, or impractical, the use of PPIs offers promise, but data from well-designed clinical trials are needed.

REFERENCES

1. Berenholtz S: Management of upper gastrointestinal hemorrhage. *Resident Reporter* 1999; 4:112–118
2. Nietsch HH: Management of nonvariceal upper gastrointestinal bleeding. *Resident Reporter* 2000; 5:38–42
3. Silverstein FE, Gilbert DA, Tedesco FJ, et al: The National ASGE Survey on Upper Gastrointestinal Bleeding: II. Clinical prognostic factors. *Gastrointest Endosc* 1981; 27:80–93
4. Lin HJ, Wang K, Perng CL, et al: Heater probe thermocoagulation and multipolar electrocoagulation for arrest of peptic ulcer bleeding: A prospective, randomized comparative trial. *J Clin Gastroenterol* 1995; 21:99–102
5. Kankaria AG, Fleischer DE: The critical care management of nonvariceal upper gastrointestinal bleeding. *Crit Care Clin* 1995; 11: 347–368
6. Friedman LS, Martin P: The problem of gastrointestinal bleeding. *Gastroenterol Clin North Am* 1993; 22:717–721
7. Gilbert DA: Epidemiology of upper gastrointestinal bleeding. *Gastrointest Endosc* 1990; 36(Suppl 5):S8–S13
8. Ritchie WP Jr: Acute gastric mucosal damage induced by bile salts, acid and ischemia. *Gastroenterology* 1975; 68:699–707
9. Moody FG, Zalewsky CA, Larsen KR: Cytoprotection of the gastric epithelium. *World J Surg* 1981; 5:153–163
10. Consensus Development Conference: Therapeutic endoscopy and bleeding ulcers. *JAMA* 1989; 262:1369–1372
11. Simoens M, Gevers AM, Rutgeerte P: Endoscopic therapy for upper gastrointestinal hemorrhage: A state of the art. *Hepatogastroenterology* 1999; 46:737–45
12. Savides TJ, Jensen DM: Therapeutic endoscopy for nonvariceal gastrointestinal bleeding. *Gastroenterol Clin North Am* 2000; 29: 465–487
13. Van Dam J, Brugge WR: Endoscopy of the upper gastrointestinal tract. *N Engl J Med* 1999; 341:1738–1748
14. Cook DJ, Guyatt GH, Salena BJ, et al: Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. *Gastroenterology* 1992; 102:139–148
15. Jaspersen D, Koerner T, Schorr W, et al: Helicobacter pylori eradication reduces the rate of rebleeding in ulcer hemorrhage. *Gastrointest Endosc* 1995; 41:5–7
16. Halm U, Halm F, Thein D, et al: *Helicobacter pylori* infection: A risk factor for upper gastrointestinal bleeding after cardiac surgery? *Crit Care Med* 2000; 28:110–113
17. Ellison RT, Perez-Perez G, Welsh CD, et al: Risk factors for upper gastrointestinal bleeding in intensive care unit patients: Role of *Helicobacter pylori*. Federal Hyperimmune Immunoglobulin Therapy Study Group. *Crit Care Med* 1996; 24:1974–1981
18. Younes Z: Medical therapies for bleeding peptic ulcer. *Resident Reporter* 1999; 4:52–56
19. Barer D, Ogilvie A, Henry D, et al: Cimetidine and tranexamic acid in the treatment of acute upper gastrointestinal-tract bleeding. *N Engl J Med* 1983; 308:1571–1575
20. Walt RP, Cottrell J, Mann SG, et al: Continuous intravenous famotidine for haemorrhage from peptic ulcer. *Lancet* 1992; 340:143–147
21. Collins R, Langman M: Treatment with histamine H_2 antagonists in acute upper gastrointestinal hemorrhage: Implications of randomized trials. *N Engl J Med* 1985; 313:660–666
22. Daneshmend TK, Hawkey CJ, Langman MJS, et al: Omeprazole versus placebo for acute upper gastrointestinal bleeding: Randomised double-blind controlled trial. *BMJ* 1992; 304: 143–147
23. Khuroo MS, Yattoo GN, Javid G, et al: A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med* 1997; 336:1054–1058
24. Schaffalitzky de Muckadell OB, Havelund T, Harling H, et al: Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers. *Scand J Gastroenterol* 1997; 32:320–327
25. Lau JY, Sung JJ, Lee KKC, et al: Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000; 343:310–316
26. Heyland D, Griffith L, Cook DJ, et al: The clinical and economic consequences of clinically important gastrointestinal bleeding in the critically ill. *Crit Care Med* 1995; 23:A108
27. American Society of Health-System Pharmacists: ASHP therapeutic guidelines on stress ulcer prophylaxis. *Am J Health Syst Pharm* 1999; 56:347–379
28. Gagnon Y, Eloubeidi MA, Arguedas MR, et al: A bigger bang for the buck: Administering intravenous proton pump inhibitors to all patients presenting to emergency with signs of acute upper gastrointestinal bleeding. Abstr. *Am J Gastroenterol* 2001; 96:S267
29. Lin HJ, Lo WC, Lee FY, et al: A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med* 1998; 158:54–58