ACUTE UPPER GASTROINTESTINAL BLEEDING

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INTRODUCTION

Gastrointestinal bleeding is a very common clinical problem. It accounts for about 300,000 hospitalizations a year (1) and many more patients will bleed during the course of a hospitalization (2). The mortality rate from upper gastrointestinal bleeding is about 8-10% and has not changed significantly over the past 40 years. This observation is deceiving, however, because the proportion of patients over 60 years of age who have been entered into studies of gastrointestinal bleeding has increased from about 6% to 48% over the same period of time (3). Patients in this age group have been shown to have a higher mortality rate (4). The high mortality rate in this age group is in great part due to comorbid conditions. Patients with underlying renal, liver, neoplastic, central nervous system, or lung disease are at greater risk of death from upper gastrointestinal bleeding (2,11). An increased incidence of peptic ulcer disease in older patients, the use of NSAIDS and a longer life expectancy probably account for a major portion of the higher proportion of older patients with upper gastrointestinal bleeding in more recent clinical trials (5).

Aging trends in patients with upper gastrointestinal bleeding (Allan et al.[7])

Series published	Patients >60 yr old (%)
1921–1936	6–17
1932–1947	24–38
1953–1973	40–48

Underlying disease versus mortality: A/S/G/E Bleeding Survey[8–10] ($p < 0.001$)

	With history (%)	Without history (%)
Renal (N = 170)	29.4	9.4
Liver (N = 488)	24.6	6.9
Neoplasm (N = 173)	24.3	9.6
Central nervous system (N = 307)	23.5	8.7
Lung (N = 394)	22.6	8.2

CLINICAL PRESENTATION

The most common clinical features of patients with acute upper gastrointestinal bleeding are hematemesis and melena. Hematemesis is vomiting of frank blood or coffee ground material. Hematemesis suggests that the lesion is proximal to the ligament of Treitz. The color of vomited blood will be red if emesis occurs soon after bleeding occurs. "Coffee ground" emesis consists of blood that has been partially acted upon by hydrochloric acid and formed precipitated blood clots within the vomitus.

Melena consists of black, tarry, foul smelling stools that should not to

be confused with black formed stools as is seen with the use of iron, bismuth, or licorice. Hematochezia usually connotes lower gastrointestinal bleeding but can be seen in massive upper gastrointestinal bleeding due to rapid transit through the gastrointestinal tract. Melena occurs only if hemoglobin remains in the gastrointestinal tract long enough to be degraded by colonic bacteria to hematin or other hematochromes which blacken the stools. About 50-100 ml of blood is required to produce a melenic stool and melena may take several days to clear after a clinically significant bleed (6,7). A minority of patients present with symptoms related to blood loss without overt hemorrhage. These patients may present with angina pectoris, dizziness, syncope, shortness of breath, or mental status changes.

INITIAL APPROACH

The first step in the management of patient with upper gastrointestinal bleeding is to perform a **rapid assessment** to determine the urgency of the situation. The blood pressure and pulse provide valuable information in making this determination. If a patient is in shock with a blood pressure of 95-100 systolic and tachycardia, then loss of 50% of blood volume may have occurred and the situation is urgent. If the patient is not in shock, blood pressure and pulse should each be determined in both the supine and upright positions. If orthostatic blood pressures are performed in the patient with shock or prominent orthostatic symptoms, it may result in a rapid decrease in cerebral perfusion. A systolic blood pressure that drops to less than 90mm Hg in the upright position suggests a 25-40% decrease in blood volume. A drop of 10mm Hg or more in the systolic blood pressure or an increase in heart rate above 120 usually indicates a 20% reduction in blood volume.

Historical features may also assist in determining the urgency of a bleeding episode. A history of repeated red hematemesis, orthostatic symptoms, hematochezia from an upper gastrointestinal source, evidence of continued blood loss, or ischemic end organ dysfunction suggests a high risk patient. In many cases, however, the activity of the bleeding is less obvious and one needs to watch for clues that the situation is more acute than initially thought.

Simultaneously with a rapid assessment, resuscitation should be carried out. The rate of volume infusion should be guided by the patient's condition, the degree of volume loss suspected, and the rate of active bleeding. The orderly sequence of taking a history, performing a physical

examination, and making a thoughtful assessment and treatment plan has to be readjusted to meet the immediate needs of the patient. Two large bore intravenous lines with 14 to 18 gauge catheters should be placed in large peripheral veins. Normal saline or lactated Ringer's solution should be used initially. Patients in shock may require rapid boluses of large volumes of fluid. Blood samples for typing and crossing, CBC, platelet count, PT, PTT, and chemistries should be sent to the lab immediately. If bleeding is massive, the blood bank should be notified of the potential demand for blood products. In some cases, non-cross matched O- blood, whole blood, or simultaneous multi-unit transfusions may be necessary. Electrocardiograms should be performed in patients with chest pain, a history of coronary artery disease, or in those over the age of 40. Supplemental oxygen may be useful in patients with severe blood loss, advanced age, or comorbid illness. Prophylactic endotracheal intubation to prevent aspiration should be considered in any patient with massive bleeding with ongoing hematemesis, especially if esophageal varices are suspected. Patients with hemodynamically significant bleeding or active ongoing bleeding should be admitted to an intensive care unit.

EVALUATION OF THE STABILIZED PATIENT

HISTORY AND PHYSICAL EXAMINATION

In many cases, the history will provide clues as to the possible etiology of gastrointestinal bleeding. Hematemesis, melena, and hematochezia have already been mentioned. A prior history of peptic ulcer disease or dyspeptic symptoms may suggest ulcer bleeding. The use of NSAIDS is also associated with peptic ulcer disease although it may precipitate bleeding from other sites or lesions within the gastrointestinal tract. A history of coughing and wretching raises the possibility of a Mallory-Weiss tear. Alcohol abuse or liver disease may suggest the need for urgent endoscopy to diagnose variceal bleeding. A history of prior bleeding episodes, coagulopathies, systemic diseases associated with gastrointestinal bleeding, or prior aortic graft surgery may all help delineate the cause of the bleeding and help plan treatment.

The physical examination may also provide critical information in evaluating patients with gastrointestinal bleeding. Stigmata of cirrhosis such as jaundice, ascites, asterixis, spider angiomas, splenomegaly, gynecomastia, and testicular atrophy suggest that varices are a likely possibility. Rectal examination will help in localizing the site of the bleeding and the stool color will help direct further evaluation.

Hyperactive bowel sounds are often seen in upper gastrointestinal bleeding. Abdominal tenderness in the epigastrium is common in peptic ulcer disease. Lymphadenopathy, Kaposi's sarcoma lesions, or abdominal masses may suggest malignancy. More unusual physical findings may include associated with hereditary vascular anomalies such as perioral telangiectasias associated with hereditary hemorrhagic telangiectasia, or blue subcutaneous nodules associated with blue rubber bleb nevus syndrome. Evidence of a polyposis syndrome such as hyperpigmented macules on the lips associated with Peutz-Jeghers syndrome or soft tissue masses associated with Gardner's syndrome may be present.

LABORATORY TESTING

The initial hematocrit in a patient with acute gastrointestinal bleeding may not reflect the degree of blood loss as plasma and RBCs are lost in the same proportions. Once the intravascular volume is restored from the extravascular compartment, the hematocrit will drop. This equilibration process may take up to 72 hours to complete and therefore a normal hematocrit can be seen on admission in patients with severe bleeding. Serial CBC's may be helpful in monitoring patients for rebleeding during the course of a hospitalization. A low mean cell volume may indicate more chronic blood loss. A low platelet count may be due to portal hypertension. Transfusions of platelets should be given in patients with active bleeding and a platelet count of less than 70,000/ul. Transfusion of blood should be considered on the basis of underlying medical problems, ongoing bleeding, or symptomatic anemia.

A prolonged prothrombin time may be due to liver insufficiency and should be corrected with fresh frozen plasma in patients with active bleeding. Subcutaneous vitamin K can be also be administered. In patients with specific factor deficiencies, as in hemophilia or von Willebrand's disease, factor replacement should be started as soon as the disorder is recognized.

An elevated BUN is often seen in upper gastrointestinal bleeding and is due to intravascular volume depletion and absorption of blood proteins (8). The serum calcium and potassium should be monitored and corrected in patients who require multiple transfusions.

NASOGASTRIC LAVAGE

If the site of the bleeding is uncertain, a nasogastric tube should be inserted as an extension of the physical examination. Bright red blood from the nasogastric tube indicates recent or active upper gastrointestinal bleeding. A negative aspirate does not rule out an upper GI source. False negative results can be due to bleeding from the duodenum that is not refluxed through the pylorus or from curling of the nasogastric tube in the fundus of the stomach. Lavage with 250-500ccs of water may increase the yield. Still, sixteen percent of patients found to have actively bleeding lesions at endoscopy will have a negative lavage (9). A "bile stained" aspirate does not rule out an upper source either since physicians are wrong half the time when they report an aspirate is bilious (10). Guaiac testing of aspirates is of no clinical value as both false negative and false positive results may occur. Unless protracted vomiting is present, the nasogastric tube can be removed after diagnostic lavage.

The character of the material obtained from the nasogastric aspirate, in conjunction with the character of the stools, has prognostic value (11). A clear aspirate is associated with a mortality of 6%, whereas coffee grounds and frank blood are associated with mortality rates of 9.7 and 20.1% respectively. Patients with a red aspirate and red stools on presentation have a mortality of 28.7%.

Nasogastric aspirate and stool color versus mortality: A/S/G/E Bleeding Survey[8-10]

	Stool color		
	Brown (%)	Black (%)	Dark red (%)
Nasogastric aspirate Color			
Clear	7.9	4.7	7.3
Coffee grounds	7.8	8.3	19.1
Red	19.4	12.3	28.7

DIFFERENTIAL DIAGNOSIS

The most common cause of upper gastrointestinal bleeding is peptic ulcer disease, with duodenal ulcers being somewhat more common that gastric ulcers. Gastric erosions, varices, and Mallory-Weiss tears make up the bulk of the rest of the cases, although their relative frequency varies somewhat depending on the population studied. For example, a large survey of the members of a national GI society found only 10.3% of

patients bled from varices (2). By contrast, a review of 445 consecutive patients with upper gastrointestinal bleeding at Los Angeles County/USC Medical Center reported a 31% incidence of varices (12).

A/S/G/E Bleeding Survey[8-10] endoscopic diagnoses

Diagnosis	% Incidence
Gastric erosions	29.6
Duodenal ulcer	22.8
Gastric ulcer	21.9
Varices	15.4
Esophagitis	12.8
Erosive duodenitis	9.1
Mallory Weiss tear	8.0
Neoplasm	3.7
Esophageal ulcer	2.2
Stomal ulcer	1.9
Oster-Weber-Rendu telangiectasia	0.5

Table 1. Sites of bleeding in 445 consecutive patients presenting with major* upper gastrointestinal haemorrhage at Los Angeles County + University of Southern California Medical Center[31]

Duodenal ulcer	120 (27%)
Gastric ulcer	57 (13%)
Varices	137 (31%)
Mallory–Weiss tear	60 (13%)
Erosive/haemorrhagic gastritis	14 (3%)
Erosive oesophagitis	8 (2%)
Vascular malformations	5 (1%)
Prolapse gastropathy	3 (1%)
Gastric cancer	3 (1%)
Other	5 (1%)
Site not identified	33 (7%)

EMPIRIC MEDICAL THERAPY

GASTRIC LAVAGE

Gastric lavage with iced saline has been performed as an initial treatment in upper GI bleeding for many years. The practice evolved from studies by Wangensteen in the late 1950s in which he demonstrated a 75% reduction in gastric acid and pepsin secretion and a 66% decrease in gastric blood flow in dogs who underwent gastric cooling using a 2-5 degree centigrade solution (13,14). This led to the development of gastric hypothermia machines and balloons which provided a large area of mucosal contact (15). This procedure declined in popularity in the 1960s due to reports of systemic hypothermia, pneumonia, thermal tissue damage and ventricular arrhythmia (16). Even so, iced saline lavage continued to be recommended by major textbooks.

Several more recent observations have mitigated against the practice of iced saline lavage. An <u>in vivo</u> study involving dogs done by Waterman and Walker demonstrated a threefold increase in bleeding times in the chilled stomachs of these animals (17). Clotting times increased 60% and prothrombin times were found to be twice normal when performed at lower temperatures (18). In other studies involving experimentally induced ulcers in live dogs, iced saline was found to be no better than room temperature at controlling hemorrhage (19,20). Thus, the use of iced saline is of no proven benefit and may be harmful.

Adding norepinephrine to lavage solutions has been advocated as a

therapy has not been shown to be of benefit. Albert, et al. found that iced saline lavage with norepinephrine did not slow bleeding significantly more than iced or warm saline in an experimental dog model (20).

ACID REDUCTION THERAPY

Acid reduction therapy has been extensively investigated as a potential therapy for ongoing, acute UGI bleeding. The rationale for this intense interest was provided by experiments which demonstrated that the environment in upper gastrointestinal tract is not conducive to effective hemostasis. Green, et al. performed in vitro studies which demonstrated a progressive increase in prothrombin time and partial thromboplastin time and an inhibition of platelet aggregation at acidic ph values (23). The effect was seen at a ph of 6.8 and progressively worsened with further decreases in ph and with the addition of pepsin. It has also been suggested that the proteolytic activity of pepsin is responsible for digesting hemostating clots once they have formed (24).

The role of H_2 antagonists and antacids in controlling active upper gastrointestinal bleeding has been evaluated in multiple trials. The single largest study was a prospective, randomized multi-center placebo controlled trial involving 285 patients which evaluated the ability of intravenous cimetidine(300 mg IV q6 hours) to stop bleeding. About twenty nine percent of patients treated with cimetidine continued to have active bleeding. The failure rate was not significantly different from the 22.7% in the placebo group (25). Moreover, when patients were separated into diagnostic categories, no significant differences were found. One hundred ninety four of the patients who stopped bleeding were also evaluated to see if oral cimetidine(300 qid), oral cimetidine plus antacids, or hourly antacids alone were better than placebo in preventing rebleeding during the course of a hospitalization. None of the regimens were more affective than placebo in preventing rebleeding(25).

No single trial has convincingly shown an overall benefit of H2 antagonists in stopping active upper gastrointestinal bleeding but several studies have claimed that certain subgroups have benefitted (e.g. duodenal ulcer or gastric ulcer patients). Collins and Langman pooled data from 27 randomized controlled trials to increase the statistical power of the available information (26). The rate of rebleeding, surgery, and death were found to be decreased by 10, 20, and 30% respectively. All of the benefit seemed to be confined to the subgroup of patients with gastric ulcers. These decreased rates were marginally statistically significant for

surgery and death and insignificant for bleeding and, therefore, the authors stated that the the study was inconclusive.

The development of more potent acid suppressive agents has led to renewed interest in the role of acid suppressive therapy in controlling UGI bleeding. Omeprazole, a proton pump inhibitor, is a powerful acid suppressant and several reports of successful cessation of gastrointestinal bleeding have been published (27-29). The ability of omeprazole to control upper gastrointestinal bleeding was investigated in a large, double-blind placebo controlled study involving 1147 patients (30). The patients in the treatment group were given 160mg of intravenous omeprazole followed by 80mG/day orally for 3 days. No significant differences were found between the placebo and omeprazole groups in regard to transfusion requirements, rebleeding, need for surgery, or morbidity.

TRANEXAMIC ACID

One theory put forth to explain continued bleeding or rebleeding in patients with upper gastrointestinal lesions is that dissolution of a formed fibrin clot is responsible. Fibrinolytic activity has been found in the gastric veins of patients with upper gastrointestinal bleeding (36) and plasminogen activators have been found in the gastric and duodenal mucosa of such patients (37). Fibrinolytic activity has also been discovered in the gastric juice of both normal patients and patients with upper gastrointestinal bleeding (38,39). These observations have led to studies of the plasminogen inhibitor tranexamic acid in controlling acute upper gastrointestinal bleeding. This agent has the added feature in that it inhibits the fibrinolytic activity of pepsin (40)

Several trials have shown that tranexamic acid is beneficial in acute upper gastrointestinal bleeding although the nature of these benefits has been inconsistent. Initial studies showed reductions in transfusion requirements and the need for surgery, but no reduction in mortality (41-43). The largest individual trial involving tranexamic acid was performed by Bauer, et. al. who, in a blinded fashion, randomized 775 patients with upper gastrointestinal bleeding to tranexamic acid, cimetidine or placebo. The 256 patients who received tranexamic acid had a 4% mortality as compared with an 11% mortality in the placebo group and an 8% mortality in the cimetidine group (44). This reduced mortality was not accompanied by a decrease in the amount of blood transfused, the rebleeding rate, or in the need for surgery. The difference in mortality was, therefore, unlikely due to gastrointestinal bleeding and remains unexplained.

Henry and O'Connell performed a meta-analysis of six randomized double blinded placebo controlled studies to attempt to draw some definitive conclusions regarding tranexamic acid (45). The analysis included a total of 1267 patients with upper gastrointestinal hemorrhage. Treatment with tranexamic acid was associated with a 20-30% reduction in the rate of rebleeding, a 30-40% reduction in mortality (45). Adverse events in the tranexamic acid group included cerebral infarction, myocardial infarction, embolism, deep vein thrombosis, and superficial thrombophlebitis. The number of such events in the placebo group was less than one third of the rate in the treatment group. Cerebral infarction has also been a problem when tranexamic acid was tried for subarachnoid hemorrhagic (46). Concern over side effects coupled with inconsistent data regarding the efficacy of tranexamic acid have limited its usage among practitioners.

SOMATOSTATIN

Somatostatin and octreotide, a long acting somatostatin analogue, was hypothesized to have a role in the management of upper gastrointestinal bleeding because it decreases gastric acid pepsin secretion (47) as well as splanchnic blood flow (38). Studies of somatostatin in acute gastrointestinal bleeding have yielded conflicting results. Some trials have shown a reduction in the number of units of blood transfused (49-51, 54), the need for emergency surgery (51, 52) and the number of patients with continued bleeding (49-54). However, in most of the trials the benefit was small and the criteria for success arbitrary. Several other trials have shown no benefit of somatostatin over placebo in any of these parameters(55-57). The two largest trials have been in the latter category. Somerville, et. al. performed a randomized, double blind, controlled trial of somatostatin versus placebo in 630 patients who presented with hematemesis and melena (55). No significant differences were found in regards to the rates of rebleeding, operation or death. The results were clouded by a high dropout rate (96 patients), the fact that some patients received tranexamic acid, and the higher proportion of patients with active bleeding or stigmata of hemorrhage at endoscopy in the placebo group (55). Christiansen, et. al. performed a double blind, placebo-controlled multicenter trial in which he randomized 273 patients to octreotide or placebo and found no significant differences in surgery rates, blood transfusion requirements, or time required before bleeding stopped between the two groups (57). It is reasonable to conclude that somatostatin and its analogue have no proven therapeutic benefit in active upper gastrointestinal non-variceal bleeding.

PROSTAGLANDINS

Prostaglandins possess a number of properties that have inspired optimism regarding its ability to control upper gastrointestinal bleeding. Prostaglandin E2 has been found in human gastric mucosa and gastric juice and has been shown to inhibit gastric acid production and stimulate mucosal blood flow and bicarbonate and mucous secretion (58a). Topical or oral prostaglandins have undergone intense scrutiny as a treatment of NSAID induced mucosal damage, but have also been evaluated in patients with ongoing nonspecific upper gastrointestinal bleeding. Raskin et. al. prospectively randomized 138 patients with hematemesis or melena due to endoscopically proven ulcerative or erosive lesions of the stomach or duodenum to receive either PGE2 or placebo (60). The percentage of patients who had stopped bleeding at 48 hours, had recurrent bleeding, or needed surgery was not different in the two groups. Two other small randomized prospective, double blind placebo controlled trials have come to the same conclusion-these agents are not effective in stopping acute upper gastrointestinal bleeding, nor do they prevent early rebleeding (58b-60). These trials involved relatively small numbers of patients, so it is possible that a marginal benefit could exist and not be statistically demonstrable because of the small sample size involved. This, however, remains to be proven.

INTRAVENOUS VASOPRESSIN

Vasopressin is a hormone produced in the posterior pituitary that functions primarily to maintain the constancy of the serum osmolality and intravascular volume. It has also been shown to reduce splanchnic blood flow and portal pressure. Very few trials of intravenous vasopressin for non-variceal upper gastrointestinal bleeding have been performed (61). Fogel, et al. performed a prospective, double-blind study in which he randomized 60 patients with active gastrointestinal bleeding to receive either a continuous intravenous infusion of vasopressin at a rate of 40 units/hour on placebo. No significant difference was found between the two groups at 6 hours or at 24 hours with regard to cessation of bleeding, need for transfusion or surgical intervention (62). About 45% of the patients in this study bled for varices, but there was no advantage to intravenous vasopressin in the nonvariceal or variceal subjects. The lack of proven efficacy and the seriousness of the adverse effects of intravenous vasopressin make this an unwise choice for empiric therapy in acute upper gastrointestinal bleeding.

SULCRAFATE

Sulcrafate is a non-absorbable aluminum salt of sucrose octasulfate that has been used to treat peptic ulcer disease and to prevent stress induced mucosal damage (65, 66). It functions as a weak antacid, has antipepsin activity, stimulates prostaglandin synthesis and forms a protective coating over inflamed areas of mucosa (114, 115). Goldfarb and Czaja performed a trial in which they openly randomized 20 patients with active upper gastrointestinal bleeding or stigmata of recent hemorrhage to either sulcrafate of cimetidine (67). The drugs had equal efficacy in controlling bleeding, but there were more side effects in the cimetidine group. However, the dose of cimetidine used was quite high (1800mg/day). The value of sulcrafate as empiric medical therapy for active upper gastrointestinal bleeding awaits proof in a blinded, randomized, placebo controlled trial.

SPECIFIC BLEEDING LESIONS AND THEIR TREATMENT

PEPTIC ULCER DISEASE

PATHOPHYSIOLOGY

Peptic ulcer disease accounts for about half of all hospitalizations for upper GI bleeding. Although the total number of hospitalizations for peptic ulcer disease in the USA has declined sharply with time, most of this decline is due to a decrease in admissions for uncomplicated peptic ulcer disease (134). Hospitalizations for bleeding gastric ulcers has actually risen almost twofold. Although the mortality rate from a single episode of gastrointestinal bleeding is 7%, a second hemorrhage is associated with a much higher mortality rate (135,159).

Bleeding from peptic ulcer disease occurs when an ulcer bed erodes into an artery in the wall of the gastrointestinal tract. Swain et al found that these vessels ranged from 0.1-1.8mm in size (average 0.7mm) and were located submucosally or in the serosa (137). Bleeding from larger vessels are harder to control. Ulcers in the posterior duodenum may erode into the gastroduodenal artery, and ulcers high in the gastric body may erode into the left gastric artery. Patients with ulcers in these ulcers may be at high risk of severe bleeding (139). Hypersecretion of acid does not appear to be more of a problem in patients with bleeding ulcers compared

to those with nonbleeding ulcers (140).

Non-steroidal anti-inflammatory drugs (NSAIDS) are associated with a higher incidence of bleeding peptic ulcers. In two separate reports, these agents were implicated in over 50% of bleeding ulcers, a much higher percentage than was found in patients presenting with pain (2,158). An increased mortality rate has been reported by some authors (160,161). These agents are most commonly associated with gastric ulcers, but duodenal ulcers are also seen with these agents. Painless bleeding has been said to be a feature of NSAID ulcers, but the lack of pain may be a function of the advanced age of many NSAID users than the drug itself(138). Corticosteroids almost double the risk of GI complications in patients taking NSAIDS compared to those taking NSAIDS alone, although corticosteroids alone do not seem to be a problem (161).

ENDOSCOPIC FEATURES

About 80% of ulcers will stop bleeding spontaneously. The goal is to identify the 20% at higher risk and intervene to improve their outcome. In addition to the clinical features mentioned above, the endoscopic appearance of an ulcer provides valuable prognostic information. Ulcers with active bleeding, a nonbleeding visible vessel, an adherent clot, a flat spot, or ulcers with a clean base all behave differently.

Patients with brisk arterial bleeding have an 80-100% rate of continued bleeding or early rebleeding if no treatment is rendered (141,142). Obviously, these patients are at very high risk and intervention is required. Patients who are slowly oozing may only have a rebleeding rate of about 33% (142).

Patients who are not actively bleeding but have a visible vessel in the ulcer base have a rebleeding rate of about 40-50% in most series (136,141,143,144). The terms "sentinel clot" and "pigmented protuberance" have been coined by those who believe that what is referred to as a vessel is sometimes actually a clot overlying a vessel in the ulcer base (136,155). These terms have been used interchangeably although a clot overlying a vessel may have a lower rebleeding rate (155).

Table 4. STIGMATA OF RECENT HEMORRHAGE: RISK OF REBLEEDING

Endoscopic Lesion	Risk of Rebleeding (%)
Active bleeding	90–100
Nonbleeding visible vessel (pigmented protuberance)	40–50
Adherent clot	20–30
Oozing without visible vessel	10
Flat spot	5–10
Clean base	1–2

Patients who are found to have an adherent clot in the base of an ulcer are reported to have a rebleeding rate in the range of 20-30% in most series, although there is quite a bit of variation in these reports (141,142). There is some debate in the literature as to whether there is a benefit to administering endoscopic treatment to this group of patients. Removal of the clot may reveal a visible vessel which has a high likelihood of rebleeding. This maneuver interferes with the natural mechanisms that have already begun to seal the vessel, however, and could precipitate bleeding. A recent consensus conference concluded that only actively bleeding vessels or visible vessels should be treated endoscopically (145). Patients with adherent clots should only be treated in this fashion in a "deteriorating clinical" situation. We are currently involved a in randomized, multi-centered trial to help solve this dilemma.

Ulcers with only a flat pigmentation spot only have a rebleeding rate of about 7%. Ulcers with a clean base have a rebleeding rate of about 3%. Fortunately most patients will be found to be in these low risk groups and can be managed outside of the ICU and discharged within 2-3 days (141).

In the future, high frequency, pulsed Doppler ultrasonography probes may be used to identify patients at risk of rebleeding from ulcers or to evaluate the success of endoscopic treatment. Bleeding was rare in patients with Doppler negative studies in one trial (146).

ENDOSCOPIC THERAPY FOR BLEEDING ULCERS

Endoscopic therapy for bleeding ulcers is indicated for patients with active bleeding or visible vessels found at endoscopy (145). There are two main types of endoscopic therapy used to treat ulcers: thermal methods and injection therapy. Thermal methods include laser therapy,electrocoagulation, and heater probe. A variety of substances have been used as injection therapy, as will be discussed below.

Thermal Methods

Laser Therapy

Laser light is absorbed by tissues and converted to heat. This heat causes vessel shrinkage and edema that compresses the vessel (148). Both the argon and Nd:YAG lasers have been employed in the endoscopic treatment of bleeding peptic ulcers. The Nd:YAG laser has been used more frequently because of its deeper penetration. Success has been variable in clinical trials, with only about half of the trials showing benefit

(143149,150). This modality has lost favor because of its lack of portability, high cost, technical difficulty and theoretical concerns over perforation.

Electrocoagulation

Monopolar electrocoagulation is widely available in most GI units and has been used as a source of heat for coagulating blood vessels. It employs a single electrode on a probe tip with a grounding pad placed on the patient to complete the electrical circuit. There is a possibility of sparking with this method, with the potential for deep tissue destruction and perforation.

With multipolar coagulation, both the positive and negative electrodes necessary to complete the circuit are on the tip of the probe. Electrical current passes between the probes, resulting in more controlled tissue destruction. The degree of tissue injury is determined by the amount of pressure placed on the tissue by the probe and the power setting of the generating unit. Pressure is applied directly to the bleeding vessel to occlude blood flow before the coagulating current is applied. This is called coaptation and is thought to promote sealing of bleeding vessels, particularly larger ones (147). Two prospective randomized controlled trials have shown multipolar electrocoagulation to be superior to sham endoscopic treatment in patients with visible vessels (144,156).

The heater probe applies heat to tissue directly. Like multipolar electrocoagulation, the depth of tissue injury relates to the power output of the generating unit and the pressure exerted by the endoscopist. The principles of its use are very similar to multipolar coagulation. In addition, both modalities are portable and not particularly hard to operate. While cheaper to operate than a laser unit, the generating units and probes are somewhat expensive.

Injection Therapy

Effective hemostasis can be achieved with a variety of solutions including epinephrine, sclerosants, 98% alcohol and even saline. These solutions are injected into and around bleeding vessels using a probe passed through the biopsy channel of an endoscope. Epinephrine produces hemostasis by causing vasoconstriction and by producing edema in the tissues surrounding the bleeding vessel. It has been shown to be effective in controlling bleeding from ulcers but many of the studies patients were

endoscoped a second time within 24 hours to look for rebleeding (154). Sclerosants and 98% alcohol cause inflammation within blood vessels as well as dehydration and shrinkage of surrounding tissues. This leads to thrombosis of the blood vessel, a feature not seen with epinephrine alone (157). Some endoscopists prefer to inject a sclerosant or employ thermal methods after using epinephrine for fear that rebleeding will occur when the epinephrine wears off. This has not clearly been shown to be of additional benefit, however (154). Injection of saline into an ulcer bed produces tamponade of the bleeding vessel-an effect that may be present to a certain degree with all forms of injection therapy.

Other Methods

The endoscopically applied hemoclip is a new modality that has been used to stop bleeding from a number of lesions within the gastrointestinal tract, including peptic ulcers. A recent uncontrolled study involving 88 patients with nonvariceal bleeding reported 100% initial cessation of bleeding with a rebleeding rate of only 6% (151). Microwave probes have also shown promise in animal models of bleeding ulcers (152). More data is needed before these techniques can be recommended with enthusiasm.

Comparing Endoscopic Therapies

Two recent meta-analyses have concluded that thermal methods and injection therapy significantly reduce recurrent bleeding and the need for emergency surgery by 60-80% when applied to patients with active bleeding or visible vessels at endoscopy (150,153). Multipolar electrocoagulation, heater probe, and injection therapy are recommended by most experts because of their safety record, ease of use, efficacy, and lower cost (145,150). There is little basis to recommend one of these modalities over another at this time. Perforation rates are less than 1% in most series. Bleeding can be worsened by these modalities in up to 35% of patients, but is controlled by further endoscopic therapy in over 95% of patients (156,162). Thus, not only are these methods effective, they are also safe.

SURGICAL AND ANGIOGRAPHIC THERAPY OF PEPTIC ULCER DISEASE

Immediate surgery is indicated for patients with rapidly exsanguinating ulcer hemorrhage or for patients who fail one or two

attempts at endoscopic hemostasis. Patients in these categories who are very poor surgical candidates should undergo angiography to embolize the bleeding vessel or receive intra-arterial vasopressin. Angiographic therapy can result in infarction or ischemia if blood flow to other vessels is compromised (162,163).

PREVENTION OF BLEEDING LATE REBLEEDING

There is some evidence that maintenance of H_2 histamine blocker therapy influences the rate of delayed rebleeding from ulcers. Jenson, et al, performed a multicenter, double-blind randomized, controlled trial involving 65 patients who had bled significantly from duodenal ulcers within the past year (33). Patients had documented healing of their ulcers by upper endoscopy and then were switched to ranitidine 150 mg at bedtime or placebo. Symptomatic recurrences were treated in both groups. They found that 36% of the patients on placebo had recurrent bleeding while only 9% on maintenance ranitidine had recurrent bleeding. Because of this profound difference, the study was stopped before all patients completed the planned three year follow up. (33). Furthermore, after the first year there was no recurrent bleeding in the ranitidine group while the risk of bleeding in the placebo group continued throughout the duration of the study, suggesting that maintenance therapy is needed for a prolonged period of time.

Recurrence of peptic ulcers after eradication of Helicobacter pylori is markedly reduced (105, 106). The role of Helicobacter pylori in decreasing duodenal ulcer rebleeding has also be evaluated in two small trials. Graham, et al. prospectively randomized 31 patients who had bled from duodenal ulcers to ranitidine alone or ranitidine plus triple therapy directed at eradiating H pylori (34). Triple therapy consisted of tetracycline 500 mg orally three times a day, metronidazole 250 three times a day and bismuth subsalicylate 5 or eight tablets daily for two weeks. Ulcer healing was documented endoscopically and no maintenance H2 blocker therapy was administered. Eradication of H. pylori was successful in 81% of patients treated with triple therapy. Ulcer recurrence was noted in 42.9% of the patients given ranitidine alone and in 17.6% of patients treated with ranitidine plus triple therapy. Rebleeding was noted in 28.6% of patients given ranitidine alone as compared to none of the patients also given triple therapy (34).

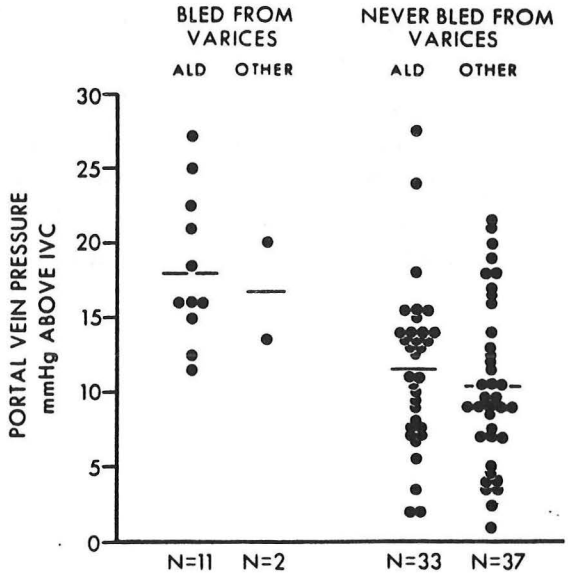
Another report involving 44 patients who had bled from peptic ulcers revealed that 33.3% of those who had persistence of H. pylori despite treatment had recurrent bleeding versus none of those in whom H. pylori was successfully eradicated (107). Larger, randomized studies are needed to confirm these preliminary findings, but eradication of H. pylori is probably prudent. Whether maintenance therapy is needed in addition to H. pylori eradication requires further study.

BLEEDING DUE TO PORTAL HYPERTENSION

The most common cause of portal hypertension is cirrhosis, although it can be due to a variety of conditions that affect portal blood flow. Persistent elevation of the portal vein pressure results in the development of collaterals from the portal to the systemic circulation. One of the routes that blood takes to bypass the liver is to go through the short gastric and coronary veins and then proceed through the periesophageal plexus to the azygous system. This produces dilated veins in the esophagus and fundus of the stomach that are called varices. Bleeding due may occur due to esophageal varices, gastric varices, or varices elsewhere in the GI tract. It may also be caused by portal hypertensive gastropathy.

Esophageal and Gastric Varices

The hepatic vein gradient is the measurement of the difference between the wedged hepatic vein pressure and the free hepatic vein pressure. This gradient is a reasonable approximation of portal pressure. Bleeding from varices is extremely rare in cirrhotic patients with a portal pressure of less than 12mm Hg (200). Further increases above this threshold does not heighten the risk any further. Isolated gastric varices may develop in patients with splenic vein thrombosis.



About 30% of patients who have esophageal varices will experience bleeding (165). Bleeding is more common when varices are large, have blue or red spots or in patients with severe liver disease (201,215). Mortality figures vary somewhat but are in the 30-50% range for each bleeding episode (165,168). One classic study of the natural history of variceal bleeding found that one third of the patients died during the initial hospitalization, another third had a second episode of bleeding within 6 weeks, and one third survived a year or more (181).

Although detailed attention to fluid replacement is essential in all patients with GI bleeding, this is even more true in patients with cirrhosis and variceal bleeding. Failure to achieve prompt replacement of volume may jeopardize renal and hepatic function-a major cause of death in these patients (166). It is equally important to avoid volume overload as this may cause severe ascites and possibly increase the risk of variceal bleeding.

PHARMACOLOGIC THERAPY

About 60% of patients bleeding from varices will stop bleeding spontaneously (198). Pharmacologic therapy for variceal bleeding should ideally improve upon this without adding to the significant morbidity and mortality inherent in the clinical situation. The most widely used agent is a continuous intravenous infusion of vasopressin. It reduces portal pressure by causing vasoconstriction of splanchnic vessels. This agent controls variceal hemorrhage in 60-70% of patients in most series. Some studies show no benefit over placebo (62,185). It is also associated with a number of undesirable side effects due to systemic vasoconstriction, such as decreased coronary blood flow, decreased myocardial contractibility, cardiac dysrhythmias, ischemic bowel disease and peripheral ischemia (63,64). These adverse effects are reduced in frequency somewhat by using intravenous or transdermal nitroglycerin at the same time (168).

Somatostatin and its synthetic analogue octreotide decrease splancnic blood flow (48) and have performed as well as vasopressin in controlling variceal bleeding (63,64). Moreover, somatostatin does not have the severe side effects associated with vasopressin and nitroglycerine is not needed (64). As previously stated, however, vasopressin has not been consistently been better than placebo in clinical trials. Somatostatin is not widely used as therapy for variceal bleeding, in part because it is very expensive.

Beta-blocker therapy with propranolol or naldolol has been shown to

decrease first bleeding in patients with esophageal varices (201). Mortality may be slightly improved and beta-blockers are particularly helpful in patients with large varices (201). Studies of patients who have bled from varices have not consistently shown reduced rates of rebleeding from beta-blockers and I do not recommend them for this indication (185,168,208,212).

ENDOSCOPIC THERAPY

All patients with suspected variceal bleeding should undergo immediate endoscopy, even if bleeding has stopped. All patients thought to have bled from varices should undergo endoscopic treatment . Gastrointestinal bleeding is obviously due to varices when active variceal bleeding is seen at endoscopy. Bleeding is also attributed to varices when a red spot or adherent clot is found on a varix or when varices are found and no other cause of UGI bleeding can be found.

Injection sclerotherapy has been the mainstay of endoscopic therapy over the years. The goal of this therapy is to control bleeding in the acute setting and to prevent rebleeding. A catheter with a retractable needle is passed through the operating channel of the endoscope. Injections are given directly into the varices in most cases, although many European centers use paravariceal injections. A variety of sclerosants are available but all work by inducing fibrosis which eradicates varices. The sclerosants are equivalent in terms of efficacy and side effects (206), but 5% ethanolamine oleate and 3% sodium tetradecyl sulphate are most commonly used in this country. Injection sclerotherapy controls acute variceal bleeding from esophageal varices in up to 95% of cases. and varices are eradicated in about 75% (168,207). Recurrent bleeding occurs in about one third of patients treated with sclerotherapy alone (209,210). While sclerotherapy has been quite effective in controlling variceal bleeding in the acute setting, it has not been consistently been shown to prevent bleeding in patients who have never bled from varices (203,204). Until the value of sclerotherapy in this situation is proven, it should not be used.

Sclerotherapy is not a benign procedure. Side effects include esophageal ulceration and stricture, chest pain, transient fever, bacteremia, pleural effusion, and portal vein thrombosis. Fortunately, severe complications such as perforation, ARDS, pericarditis, brain abscess, and sepsis are rare (164).

Table 3. Complications of endoscopic sclerotherapy

Common/occasional	Uncommon
Oesophageal ulcer	Perforation
Pain	ARDS
Fever	Pericarditis
Bacteraemia	Brain abscess
Pleural effusion	Paralysis
Oesophageal stricture	Sepsis
Oesophageal ulcer bleeding	Bacterial peritonitis
Portal vein thromobosis	

Endoscopic variceal ligation was developed as an alternative to sclerotherapy because of the high complication rate of sclerotherapy. This technique is similar to band ligation of hemorrhoids and is achieved by placing elastic bands directly onto the target varix. The bands are placed one at a time so an overtube is placed to allow easy repeated esophageal intubation. Three randomized trials have found banding as good or better than sclerotherapy in controlling bleeding (170-172). Banding ligation also eradicated varices in fewer sessions than sclerotherapy. Banding was associated with fewer complications than sclerotherapy in two of the three trials (170,172). Chest pain and dysphagia due to luminal obstruction are the most common complaints. Thus, banding appears to be a safe and effective alternative to sclerotherapy.

Gastric variceal bleeding poses a particular problem because it is not reliably controlled with sclerotherapy or banding. Gastric varices near the esophagogastric junction or within a hiatal hernia may be amenable to treatment by banding or sclerosis, but alternative endoscopic treatments have been proposed for fundic varices.

The tissue adhesives N-butyl-2-cyanoacrylate (histacryl) and isobutyl-2-cyanoacrlate (butcrylate) have been used with some success, with control of acute bleeding in over 90% of patients (173,197). However, tissue adhesives may due permanent damage to endoscopes and embolization of the glue has occurred. Most experts only revert to their use in life threatening situations (199).

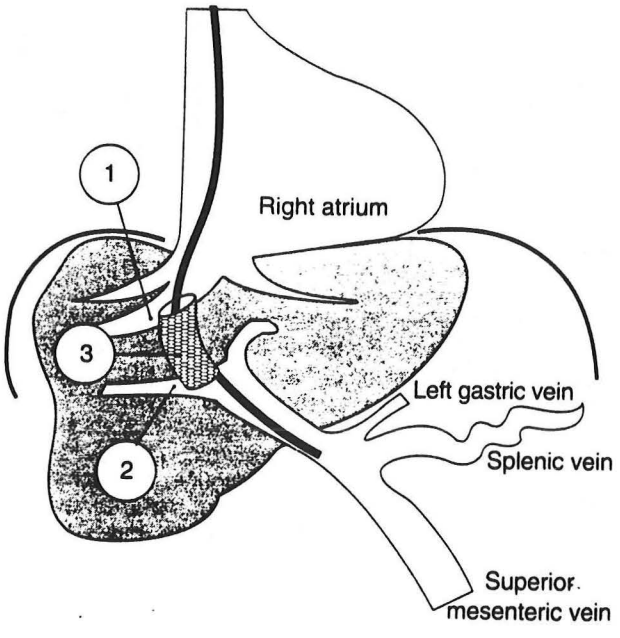
Bovine thrombin has been injected into gastric varices in an attempt to control bleeding. In a recent uncontrolled report, bovine thrombin controlled bleeding from gastric varices in eleven consecutive patients (174). More and better data is needed before this therapy can be recommended as standard treatment.

BALLOON TAMPONADE

In experienced hands balloon tamponade controls bleeding in 90-95% of patients (176). However, up to 60% of patients rebleed when the balloon is deflated (168). There is an associated complication rate of 25-30% (174), including esophageal perforation or ulceration and aspiration pneumonia. Alternative, definitive treatment must be planned for when the balloon is deflated.

RADIOLOGIC THERAPY

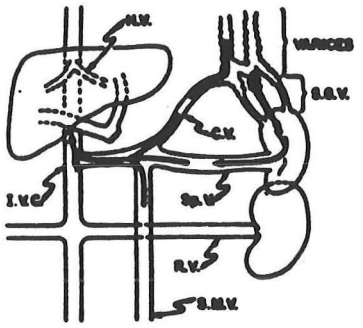
Transjugular intrahepatic portosystemic shunts (TIPS) is a valuable addition in controlling variceal bleeding. This technique involves the angiographic placement of an expandable metal stent from a branch of the hepatic vein through the liver parenchyma and into a branch of the portal vein (see below,ref 205). The goal is to lower the portal pressure below the threshold for variceal bleeding, i.e. 12mm Hg. Technical success is achieved in over 90% of patients. Active variceal bleeding can be controlled in over 90% of patients with TIPS, although it recurs in 10-20% at one year (178,205). The major complications of TIPS are associated with the creation of a porto-systemic shunt. Encephalopathy has developed in up to 25% of patients. This is seen more frequently with 10mm caliber shunts than the smaller 8mm caliber ones. Shunt stenosis occurs in up to 15% of patients and occludes completely in about 10% (178). Shunt stenosis may be managed by balloon dilation of the stent or with further stent placement. Other complications include intraabdominal hemorrhage, migration of the stent, liver infarction, and portal vein thrombosis. TIPS may be most valuable in patients who fail sclerotherapy and are not candidates for decompressive surgery due to severe liver disease, or for patients who bleed while awaiting liver transplant..



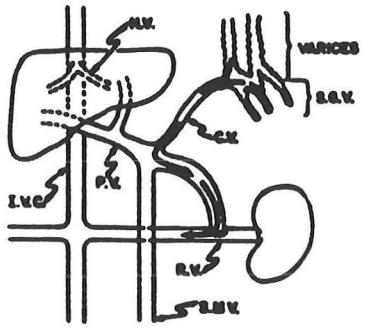
SURGICAL THERAPY

A variety of portal-systemic shunting operations have been described that are designed to create a less dangerous path for portal blood to return to the systemic circulation. Surgery provides excellent control of variceal bleeding but is associated with significant morbidity. Blood flow to the liver is compromised to some degree with all shunting surgeries and can lead to hepatic decompensation. An important study compared distal splenorenal shunt surgery to sclerotherapy with shunt surgery only performed for sclerotherapy failures (182). Only 3% of the patients who received early surgery rebled as opposed to 35% of the sclerotherapy group who required shunt rescue to control bleeding. Mortality was 22% higher in the patients who went directly to surgery, primarily due to a deterioration of hepatic function (182).

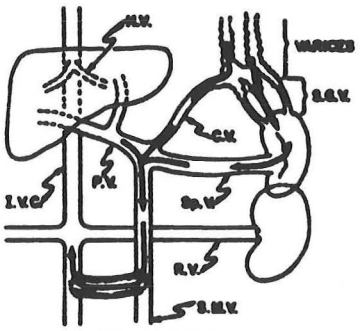
The selective distal splenorenal shunt was developed in hopes of preserving blood flow and decreasing the rate of encephalopathy with surgery. Encephalopathy rates have not been reduced, however, because of a high incidence of reversal of portal blood flow over time (182). Another limitation of this procedure of this procedure is that it is technically demanding and carries a high perioperative mortality in the emergency situation (179). In patients who are candidates for liver transplantation, however, surgery that avoids the hilum of the liver, such as the distal splenorenal or mesocaval shunt, is preferable.



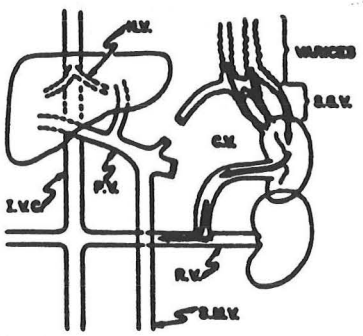
END TO SIDE
PORTAL-CAVAL SHUNT



SPLENO-RENAL SHUNT



MESO-CAVAL SHUNT



DISTAL SPLENO-RENAL SHUNT

Another surgical procedure, transection of the esophageal varices with splenectomy and extensive devascularization of the esophagus and stomach (Sugiura procedure), has met with some success in Japan. This surgery and its modifications have been somewhat less successful in this country (213,214).

TRANSPLANTATION

While the therapies mentioned above may help reduce bleeding from varices, none improve overall mortality. Mortality is determined by the severity of the patient's liver disease. Consideration should be given to transplant in patients with advanced cirrhosis.

Ectopic Varices

Varices found at other sites account for about 3% of patients with variceal hemorrhage (180). Varices may be found in the small bowel, colon or rectum. They may also be found at sites of previous surgery, within the peritoneum, and in association with the biliary tree. The treatment for ectopic varices is primarily surgical although successful control of bleeding has been reported with injection sclerotherapy (211).

Portal hypertensive gastropathy (PHG)

This condition is a vasculopathy caused by chronic passive congestion and characterized by ectatic, thick walled vessels. It is a source of chronic blood loss and does not cause brisk bleeding. Beta-blockers have been shown to reduce bleeding from PHG (202). Shunt surgery also controls bleeding due to portal hypertension, but is usually not performed for this indication.

SUMMARY

In summary, patients with acute variceal bleeding should undergo band ligation or sclerotherapy initially. If bleeding recurs and the clinical situation permits, a second attempt at endoscopic control can be made. If bleeding is not controlled endoscopically, pharmacologic therapy with vasopressin/nitroglycerin or somatostatin should be tried. If bleeding still

persists, TIPS or shunt surgery should be employed. If at any time during scenario torrential bleeding occurs, balloon tamponade therapy should be employed and plans made for more definitive treatment.
Patients whose bleeding is controlled with endoscopic therapy should be enrolled in a program of banding or sclerotherapy to obliterate their varices. After varices are obliterated, patients should undergo endoscopy every 4-6 months and have repeat obliteration if varices have recurred. Patients who fail obliteration for any reason should be considered candidates for shunt surgery or TIPS.

Patients with gastric variceal bleeding may benefit from endoscopic treatment but are candidates for shunt surgery or TIPS. Patients with isolated gastric varices due to splenic vein thrombosis are cured by splenectomy.

STRESS INDUCED MUCOSAL DAMAGE

The term "stress gastritis" has often been used to describe gastric superficial hemorrhages and erosions that are seen in patients who are critically ill. The word "gastritis" is inaccurate, however, as the condition is not associated with a histologic cellular inflammatory infiltrate (68). A simple description of endoscopic findings or use of the term stress induced mucosal damage (SIMD) is more appropriate. Use of alcohol or non-steroidal anti-inflammatory agents can produce histologically identical lesions (68) Seventy five to 100% of patients will have SIMD if endoscoped after severe physiologic stress (69, 70), but only 5% to 20% will develop clinically significant gastrointestinal bleeding (71, 72). Massive bleeding is seen in only 2-5% of patients and implies the lesions have penetrated beyond the muscularis mucosa (68, 72). SIMD is thought to be primarily due to an ischemic insult to the gastric mucosa which compromises its ability to ward off damaging effects of intraluminal acid (73-75).

Table 10.2. Risk Factors for Stress-Related Erosive Syndrome

1. Large (>50%) body surface area burns
2. Intracranial lesions associated with coma
3. Major trauma
4. Fulminant hepatic failure
5. Shock
6. Sepsis
7. Acute respiratory failure requiring prolonged mechanical ventilation
8. Acute renal failure
9. Coagulopathy

ACTIVELY BLEEDING LESIONS

Acute gastrointestinal bleeding from SIMD can cause significant morbidity and mortality. Moreover, if medical and endoscopic therapy fail, a total gastrectomy is usually needed and this carries a mortality of 40-50% (134). Physicians confronted with this grim prospect have tried a number of medical therapies in refractory cases.

Acid reduction therapy has been evaluated to a limited degree. There is data from large, randomized, controlled trials that examined the value of H2 histamine blockers in patients with acute gastrointestinal bleeding from all etiologies (19, 23). Subset analysis in these large trials failed to demonstrate any benefit of H2 blockers or antacids in controlling active bleeding from SIMD (19, 23). There have been several reports of omeprazole in controlling active bleeding from SIMD (76, 77, 84). However, a large, prospective, randomized double blind study designed to evaluate patients with active upper gastrointestinal bleeding from any source failed to show any benefit of the drug in the subset of patients with SIMD (33). There is one uncontrolled report of cessation of bleeding in 23 of 25 patients with massive bleeding from SIMD who were given antacids titrated to keep the gastric ph at 7.0 (135).

Sulcrafate given in high doses (up to 24 grams per day) was reported to stop bleeding in 10 patients bleeding from SIMD that was refractory to treatment with H2 histamine antagonists and pirenzepine (78). Further study is needed before this regimen can be recommended.

There have also been several case reports of cessation of active bleeding from SIMD with prostaglandins (79-81). A multicenter, prospective, double blind placebo controlled study consisting of 159 patients with clinically significant bleeding patients failed to demonstrate any difference in transfusion requirements, need for surgery, or in endoscopic appearance between misoprostol and placebo (82). Several other agents, such as somatostatin, secretin and pirenepine and intravenous vasopressin have been tried with reported success, but none is of proven value in controlling active bleeding from SIMD (78, 83, 85).

PREVENTION OF BLEEDING FROM SIMD

Since there are no reliable medical or endoscopic therapies available for SIMD, prevention of bleeding from SIMD is the best option. Numerous studies have been performed over the last 20 years to test the efficacy of various prophylactic agents in attaining this goal. The studies involve a

heterogenous group of patients and in many cases include patients with clinically insignificant bleeding or use nonspecific indications of bleeding, such as guaiac positive nasogastric aspirates (89). Moreover, guaiac positive nasogastric aspirates are insensitive (86) and cimetidine has been shown to produce a false positive reading (87, 88). The most popular agents have been those directed at acid reduction, acid neutralization or cytoprotection.

ANTACIDS

Early studies of SIMD prophylaxis compared antacids to placebo. McAlhaney, et al. randomized 48 patients with more than 35% total body burns to receive either antacids titrated hourly to keep the gastric pH above 7 or no antacid (108). Only one of the 24 patients (4%) who received antacid therapy developed significant upper gastrointestinal hemorrhage, where as 7 out of 24 patients (29%) receiving no antacid developed gastroduodenal complications. Hastings, et al. randomized 100 patients with sever illness from a variety of causes to hourly antacids titrated to keep the gastric pH above 3.5 or to no prophylactic therapy (109). Two of the 51 patients (4%) who received antacid bled as compared to 12 of the 49 patients who received no antacids (24%). Several other trials subsequently showed a benefit of antacid therapy in the prevention of bleeding from SIMD (110). Antacid therapy directed at keeping the gastric pH consistently above 3.5 has been shown to be effective in preventing SIMD as compared to placebo.

H_2 ANTAGONISTS

The value of H2 antagonists as prophylactic therapy for SIMD has also undergone investigation. In a double-blind, controlled study, 50 patients with severe head injuries were randomized to therapy with either intravenous cimetidine 300mg every four hours or placebo (111). Thirty-three percent of the control group required 2 or more transfusions as compared to only 7% of the treatment group. Another small study yielded similar results (112). Groll, et al. randomized 221 patients to placebo or intravenous cimetidine (1200mg per day), and found no statistical difference in bleeding between the two groups (113). Twice as many patients bled in the placebo group, 10% versus 5% in the treatment group, but this result did not reach statistical significance because of the overall low rate of bleeding in placebo group. Overall, H2 antagonists been shown to be superior to placebo in preventing bleeding from SIMD (90). The dosages of H2 antagonists in clinical trials varies widely. Continuous infusions of H2 antagonists provide better pH control than bolus therapy

(97, 98).

SULCRAFATE

Sulcrafate has not been directly compared to placebo since trials investigating its value in preventing bleeding from SIMD followed trials which found antacids and H2 antagonists to be superior to placebo. Untreated control groups have been rejected by most investigators for ethical reasons. It has been evaluated in comparison to histamine blockers and antacids, however, and this will be discussed below.

PROSTAGLANDINS

Prostaglandins have not been impressive in preventing bleeding from SIMD in clinical trails to date. Van Essen and associates, in a prospective, double-blind, controlled trial, compared the effectiveness of prostaglandin E2 (0.5mg given via nasogastric tube every 4 hours) to placebo in preventing bleeding of SIMD (117). There was no statistically significant difference in the rate of bleeding between the two groups. Prostaglandin E2 was compared to antacids in another prospective randomized trial of patients admitted to a respiratory care unit (103). Patients received either 100mcg PGE2 every four hours or hourly titration of the gastric juice to a pH of 3.5 with antacid. Three of 22 patients (14%) in the antacid group bled in contrast to twelve of 24 patients in the prostaglandin group (50%). One however, of the parameters used to connote treatment failure was hemoccult slide test for occult blood-a clinically unimportant and unreliable endpoint (86). Another prospective, double-blind, double-placebo trial compared misoprostol 200 mcg every four hours with antacid titrated to maintain the gastric pH above four in 281 patients scheduled for major surgical procedures (118). No clinically significant upper gastrointestinal hemorrhage occurred in either group and the authors concluded that misoprostol (a prostaglandin E1 analogue) was as effective as antacids in preventing bleeding from SIMD (118). While this may be the case, it is also possible that the population evaluated was not a significant risk for developing bleeding from SIMD. The value of prostaglandin therapy in preventing bleeding from SIMD remains to be established.

OTHER THERAPY

Other agents such as the anticholinergic agent pirenzepine (99), dimethylslulfoxide (100), vitamin A (110) and enteral nutrition (101) have been reported to protect patients from bleeding with SIMD. The benefits of these agents await confirmation in large, prospective, controlled trials.

Individual trials have given somewhat inconsistent results in regards to the relative benefits of prophylactic agents, so in recent years several meta-analyses have been performed. Shuman, et al. analyzed data from 16 prospective trials involving 2133 patients that compared the effectiveness of antacids, cimetidine, and placebo in the prophylaxis of bleeding from SIMD in morbidly ill patients from variety of causes (90). Patients given placebo bled overtly 15% of the time, while those given antacids and cimetidine bled overtly 3.3% and 2.7% of the time respectively (90). Antacids and cimetidine were significantly better than placebo, but not compared to each other when only overt bleeding was considered.

Sulcrafate is another agent that has been used as prophylaxis of bleeding from SIMD. In individual trials sulcrafate is at least as effective as antacids or H2 histamine blockers in this regard (91-94). A recent meta-analysis reviewed 42 randomized clinical trials that compared the ability of prophylactic drugs to prevent gastrointestinal bleeding (89). There was a 50 percent reduction in relative risk of clinically important bleeding among patients receiving prophylaxis as compared to those who received placebo. There was no statistically significant differences between sulcrafate, antacids or H2 histamine blockers in preventing clinically significant bleeding (89). Another large meta-analysis by Trypa (102) analyzed 45 trials comparing these agents and came the same conclusion. The mortality rate is significantly higher in patients with bleeding SIMD. In a recent study, the mortality rate was 48.5% in a group of patients with significant bleeding from SIMD as compared to 9.1% in those without bleeding (95). Mortality in that study, as in numerous other studies, was not affected the administration of prophylaxis (96, 102).

SIDE EFFECTS OF BLEEDING PROPHYLAXIS

Antacids, H_2 antagonists, and sulcrafate are the most frequently used agents for the prevention of bleeding from SIMD. Since the value of these agents in preventing bleeding from SIMD has been demonstrated, the side effect profile of these agents is increasingly important in choosing a regimen. Antacids are effective as prophylactic agents when the

intraluminal pH is kept above 3.5 to 4.o. Titration of antacids to achieve this goal requires frequent administration and monitoring of gastric pH-a time consuming endeavor. Magnesium based antacids may cause diarrhea, interfere with the absorption of other medications, or may cause hypermagnesimia in patients with renal failure. Aluminum containing antacids may cause hypophosphatemia and bind a number of drugs in the intestinal lumen, including thyroxine and tetracycline.

Histamine H_2 receptor antagonists also have potential adverse effects. Bradycardia, hypotension and negative inotropic effects have been described with these agents, particularly with rapid intravenous infusion (120-122). These changes are probably clinically insignificant, but some authors recommend avoiding them in patients with sepsis or hemodynamic instability (123, 124). Mental confusion has been described with cimetidine, ranitidine and famotidine (124). This is most often seen in elderly patients on cimetidine who have high blood levels of the drug, usually in the setting of liver or renal dysfunction (123). Bone marrow suppression, reversible increases in liver function tests, and bronchoconstriction have also been described. All of these adverse reactions occur in less than 1% of treated patients (124). Cimetidine binds the cytochrome P-450 system of the liver and impairs the elimination of several drugs that are commonly used in the intensive care setting, such as warfarin, theophylline, phenytoin, and procainamide (123). Ranitidine binds 5 to 10 fold less avidly to the cytochrome P450 system and thus alters the metabolism of these drugs to a much lesser degree (124). Sulcrafate is associated with constipation and the absorption of H2 antagonists, phenytoin, tetracycline or other medicines may be reduced if given orally.

A great deal of concern has been raised by an increased rate of nosocomial pneumonias in patients given acid reduction as prophylaxis for SIMD. One of the major teleologic functions of gastric acid is the killing of ingested bacteria. Only Helicobacter pylori is able to survive in this environment and most cultures gastric aspirates are sterile. It has clearly been shown that treatment with antacids or H2 antagonists allow overgrowth of gram negative bacteria (125,126). Aspiration of gastric contents into the respiratory tract occurs (127), even in patients with endotracheal tubes (128). Indeed, patients with endotracheal tubes are at increased risk of developing nosocomial pneumonia. Because it has no effect on gastric pH, some experts believe it should be the preferred prophylactic agent for SIMD.

Studies have yielded conflicting results when sulcrafate has been

compared to H_2 antagonists or antacids with regard to the rates of nosocomial pneumonia. Driks, et al., randomized 130 patients to receive either to sulcrafate or to "conventional" therapy with H2 antagonists, antacids, or both antacids and H2 blockers (125). The patients in the sulcrafate group had fewer bacteria in gastric aspirates, pharyngeal swabs and tracheal aspirates compared to the other groups. There were fewer cases of pneumonia in the sulcrafate group as compared to the antacid/H2 antagonist group, 11.5% and 23% respectively, but, this did not reach statistical significance (125). Only 5.9% of patients treated with H2 antagonists alone developed pneumonia, suggesting aspiration played a role. A large retrospective trial involving 233 ventilated patients found over twice the rate of nosocomial pneumonia in patients given antacids or H2 blockers for SIMD prophylaxis compared to a group given sulcrafate (131). A prospective trial of 114 critically ill, mechanically ventilated patients were randomized to sulcrafate or a continuous infusion of cimetidine (130). No differences in the rate of nosocomial pneumonia was found between the two groups. A recent meta-analysis concluded that SIMD prophylaxis with sulcrafate showed a trend toward decreasing the rate of pneumonia (132). The odds ration was 0.55. The authors cautioned against drawing firm conclusions based on their analysis because many of the studies analyzed were not blinded and the characteristics of patients were inadequately reported (132). A large prospective randomized trial is needed to settle this issue.

A recent prospective multi-center study found that clinically important bleeding from SIMD occurs in less than one percent of patients unless they have a coagulopathy or require mechanical ventilation (133). Withholding prophylaxis from low risk patients would certainly lead to fewer complications from such therapy.

Mallory-Weiss Tears

A Mallory-Weiss tear (MWT) is a mucosal laceration of the gastric cardia or gastroesophageal junction. The lesions are usually about 1-2cm long. They account for about 15% of cases of UGI bleeding in most series. Mallory-Weiss tears are thought to be due to transient large pressure gradients between the intrathoracic and intra-abdominal compartments which result in lifting and stretching of the EG junction. The classic presentation is one of repeted vomiting or wretching followed by hematemesis, but these lesions have also been associated with trauma, straining at stool, primal screaming, asthma, heavy lifting, hicccups, childbirth, cardiopulmonary resuscitation, and EGD. No inciting cause is found in about half of the cases. Binge drinking of alcohol prior to

presentation is common (164,216).

Endoscopy reveals a single tear in 90% of cases. Management is usually supportive since bleeding stops spontaneously in over 90% of cases. In patients in whom bleeding does not stop spontaneously, endoscopic therapy can be employed. Both injection and thermal methods have been successfully used, but venticular tachycardia has been reported with injection of epinephrine into a MWT (218). This may be more likely to occur with esophageal injection of epinephrine because the drug may gain access to the systemic circulation via the azygous system, thus avoiding a potentially protective "first pass" effect through the liver. Angiographic therapy with embolization or intra-arterial vasopressin is successful in about 70% of patients and should be considered for patients who fail endoscopic therapy (217). Surgical oversew of the lesion is curative but is required in only 2% of cases.

Esophagitis and Esophageal Ulcers

Esophagitis and esophageal ulcers a rare cause of severe upper gastrointestinal bleeding. Acid reflux is responsible for most cases of ulcerative esophagitis but other risk factors include sclerotherapy induced ulcers, Barrett's ulcers, pill-induced damage, neoplasms, or infectious agents such as CMV or herpes. Bleeding is usually self-limited but endoscopic therapy may needed in selected cases.

Neoplasms

Benign or malignant neoplasms rarely cause severe UGI bleeding. When his does occur, surgery is the best therapy. If the patient is not a surgical candidate, then endoscopic or angiographic methods may be employed.

Angiodysplasia

Angiodysplasias or vascular ectasias are an infrequent cause of UGI bleeding, accounting for less than 5% of cases. The etiology of these lesions in the upper GI tract is uncertain. There are a number of associated conditions such as advanced age, chronic renal failure, Osler-Weber-Rendu syndrome, Ehlers-Danlos syndrome, blue rubber bleb syndrome, and the CREST syndrome.

The diagnosis is made endoscopically by finding characteristic punctate, red lesions with distinct borders. Often there are additional lesions more distal in the GI tract. When these lesions are found in the antrum in a tiger stripped pattern, a "watermelon stomach" is said to be present. Blood loss is usually slow but many patients are transfusion dependent. Osler-Weber-Rendu and chronic renal failure lesions may respond to therapy with 0.05mg ethinyl estradiol and 1.0mg of norethindrone (219-221). Endoscopic therapy with laser, heater probe, or bicap is often successful. Antrectomy should be considered for patients with watermelon stomach confined to the antrum who fail more conservative therapy.

Dieulafoy's lesion

Dieulafoy's lesion is an unusually large superficial submucosal artery that erodes through the mucosa without any associated ulceration. It is a rare cause of UGI bleeding but bleeding is usually severe. It can be difficult to diagnose because of the punctate nature of the lesion and the large amount of associated bleeding. A second or third endoscopy is required to make the diagnosis in 30-50% of cases. About 86% of these lesions are within 6cm of the EG junction, but they have been described throughout the upper and lower GI tract. In two recent nonrandomized studies, bleeding from this lesion was successfully controlled with endoscopic therapy in 85-95% of patients (222,223).. Patients who fail endoscopic therapy should undergo wedge resection or oversew of the lesion.

Hemobilia and Hemosuccus Pancreaticus

Hemobilia is strictly defined as bleeding originating from the biliary tract, although it is commonly used to describe any bleeding traversing the ampulla. Hemorrhage from the pancreatic duct has been termed hemosuccus pancreaticus but is also referred to as pancreatic hemobilia. Patients most often present with melena. The hepatic arteries and bile ducts are very close together and hemobilia is associated with trauma, surgery, invasive procedures, infections, stones, or tumors that affect the biliary tree or gall bladder. Hepatic artery aneurysms may also produce hemobilia. Unless bleeding is seen to be emanating from the ampulla, the diagnosis is made angiographically. Trancatheter embolization with Gelfoam or coils has been reported to be successful in small clinical trials.

Aortoenteric Fistulas

Aortoenteric fistula is a rare but potentially deadly cause of upper gastrointestinal bleeding. These fistulas may occur at various points in the gastrointestinal tract, but most occur in the third portion of the duodenum. The majority of aortoenteric fistulas occur in patients who have had prior Dacron graft surgery. Primary fistulas may occur in association with atherosclerotic or mycotic aneurysms. In patients with grafts in place, the fistulous tract may be at the suture line or into the graft itself. Gastrointestinal contents may contaminate the prosthesis and produce sepsis with positive blood cultures.

Bleeding from AEFs has a characteristic pattern. The initial, or so called herald bleed, is brief and usually stops spontaneously; presumably due to duodenal spasm or clogging of the fistula with clots. This is followed by massive GI bleeding in the ensuing hours or days. Thus, there is a window of opportunity to intervene after the herald bleed. Patients with aortic grafts who present with GI bleeding should be presumed to have a fistula until proven otherwise. Emergency endoscopy with a long scope is indicated in all patients with aortic grafts and GI bleeding. This may rarely show duodenal invasion by the graft, but is primarily indicated to look for other potential causes of the bleeding. CT scanning demonstrating air bubbles in the wall of the aorta or evidence of perigraft infection suggests the the presence of a fistula. In one study CT, had a sensitivity of 94% and a specificity of 85% (224). Angiography may not confirm a fistula unless there is active bleeding. In one study was only positive in one of 24 patients who had bleeding from AEFs (225)

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