Gastrointestinal bleeding - A Parkland/UTSW experience

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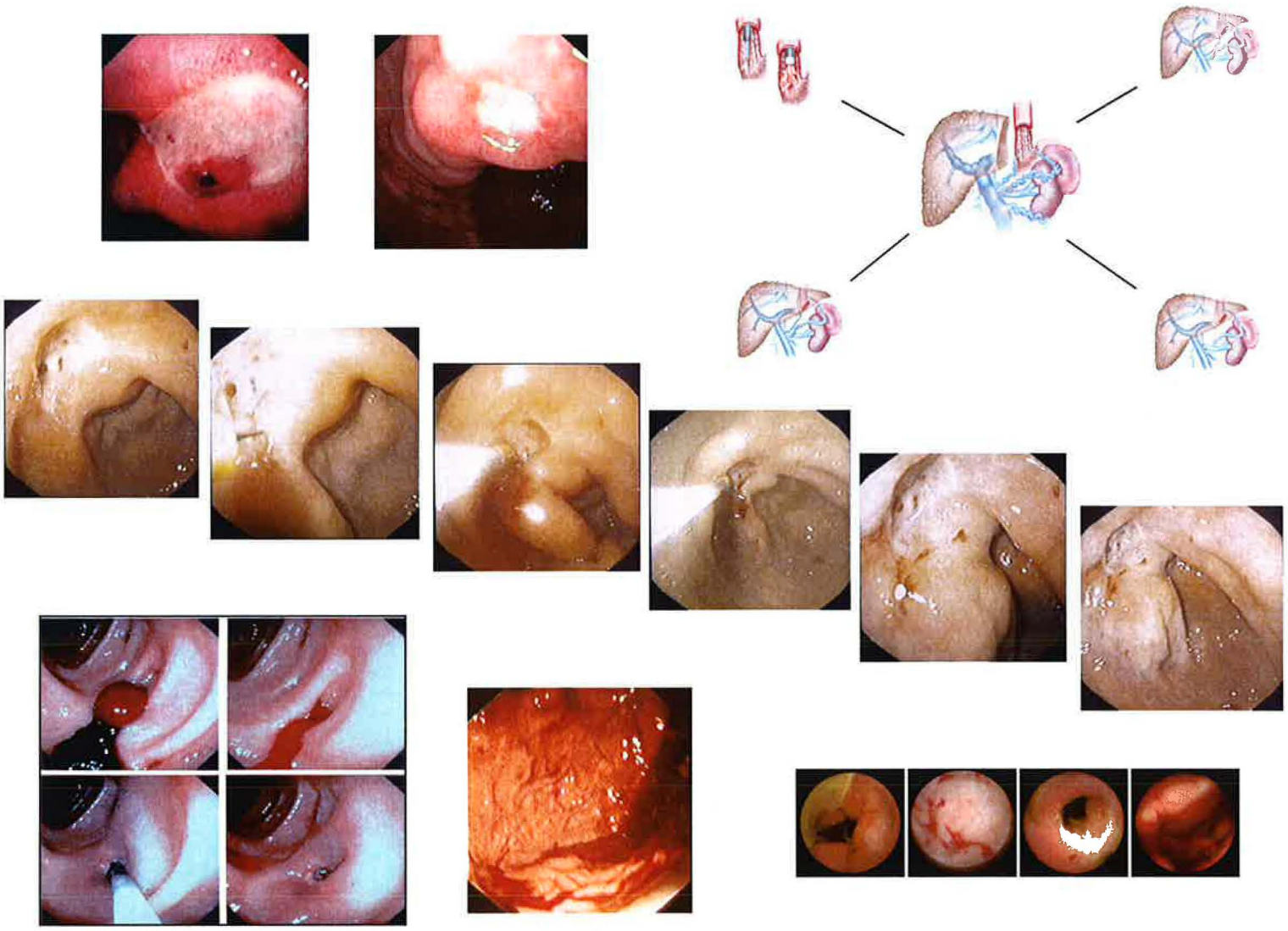

Dr. Rockey has no financial interests or other relationships with commercial concerns related to this program. Dr. Rockey will not be discussing off-label uses of drugs in his presentation.

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Dr. Rockey's clinical research focus has been to help establish national management guidelines for patients with common gastrointestinal problems. One specific area of interest has been in the area of gastrointestinal bleeding. Specific effort has been directed at determining optimal management strategies for patients with upper, lower, and occult gastrointestinal bleeding. Emphasis has additionally been on quality improvement. The second major area of interest has been in developing management guidelines for evaluation of the colon, an interest that evolved from work in patients with fecal occult blood. This work has focused on the role of colon imaging tests including air contrast barium enema, computed tomographic colonography (virtual colonoscopy), and colonoscopy.

I. Introduction

The clinical spectrum of gastrointestinal bleeding encompasses many different scenarios. The reason for its diversity is that bleeding can occur from multiple different lesions and many sites in the gastrointestinal tract. Further, bleeding may be massive or trivial, obvious or hidden. Gastrointestinal bleeding is manifest clinically in one or more of the four following manners: (1) upper, (2) lower, (3) occult, i.e., unknown to the patient, or (4) obscure—meaning from an unknown site in the gastrointestinal tract. Patients with occult and/or evident but obscure bleeding are particularly challenging since they are unaware of bleeding, or the bleeding is difficult to diagnose accurately, or both.

Gastrointestinal bleeding results in over 300,000 hospitalizations annually in the United States [2]. Bleeding from the upper gastrointestinal tract is approximately five times more common than from the lower gastrointestinal tract [3, 4]. It is more common in men and elderly persons [3, 4].

Despite a number of recent advances in the management of patients with gastrointestinal bleeding, several fundamental clinical principles remain constant, the most important of which is immediate assessment and stabilization of the patient's hemodynamic status. Thereafter, one must (1) determine the source of bleeding, (2) stop active bleeding, (3) treat the underlying abnormality, and (4) prevent recurrent bleeding.

II. Clinical Presentation

In general, the clinical signs of gastrointestinal bleeding reflect the site, etiology, and rate of bleeding. Blood loss from the gastrointestinal tract is manifest in one or more ways. *Hematemesis* is defined as the vomiting of blood and indicates an upper gastrointestinal site of bleeding, almost always proximal to the ligament of Treitz. Such blood may be either fresh, bright red blood, or it may be old and take on the appearance of coffee grounds. *Melena* is defined as passage of black, tarry, and foul-smelling stools. The black, tarry character of melena is due to degradation of blood to hematin or other hemochromes by bacteria and should not be confused with the greenish character of ingested iron or the black, nonfoul-smelling stool caused by ingestion of bismuth (i.e., in compounds such as bismuth subsalicylate [Pepto-Bismol]). *Hematochezia* refers to passage of bright red blood from the rectum that may or may not be mixed with stool. *Occult* bleeding denotes bleeding that is not apparent to the patient and results from small amounts of bleeding. Bleeding of *obscure* origin can be occult or obvious (e.g., manifest by hematemesis, melena, or hematochezia), but from a source that is difficult to pinpoint on routine examination.

Initial Patient Assessment

The first step in treating all patients with gastrointestinal bleeding is to assess the severity of bleeding. Therefore, hemodynamics is the initial focal point (Table 1) and the basis for assessment of the patients' overall clinical condition. Not only does immediate and ongoing assessment of the vital signs help focus resuscitation efforts, it also provides important prognostic information and helps triage patients toward appropriate intervention. For example, patients with unstable vital signs are often bleeding from major vascular sources such

Table 1. Hemodynamics, Vital Signs and Blood Loss

Hemodynamics Vital Sign	Blood Loss (Fraction of intravascular volume)	"Bleed type"
Shock (resting hypotension)	20-25%	Massive
Postural (Orthostatic tachycardia/ hypotension)	10-20%	Moderate
Normal	< 10%	Minor

as an ulcer with a visible vessel or gastroesophageal varices; moreover, the prognosis of these patients is poorer than that of those with normal vital signs.

RESUSCITATION

The vigor of resuscitation should be ~~is~~ proportional to the severity of bleeding. Two large-bore intravenous catheters should be placed immediately in patients who are hemodynamically unstable. Colloid (normal saline or lactated Ringer's solution) is infused as rapidly as the patient's cardiovascular system will allow. The goal is to restore and maintain normal vital signs. Intensive care unit (ICU) monitoring is indicated in hemodynamically unstable patients. Administration of supplemental oxygen by nasal cannula or facemask is indicated in most patients. Vital signs and urine output should be monitored closely, and in selected situations (for patients with underlying cardiopulmonary disease), central venous monitoring is helpful. Aggressive ICU monitoring and resuscitation is of paramount importance since implementation of this approach may decrease mortality [5].

The decision to transfuse the patient with gastrointestinal bleeding is often complicated, requires understanding of all aspects of the clinical situation, and in many cases winds up being arbitrary. Virtually all patients with unstable vital signs should be transfused, and if the patient has subnormal tissue oxygenation, transfusion should be aggressive. This principle applies also to patients who are likely to have gastrointestinal lesions that bleed massively. During resuscitation, patients with continued instability in vital signs, containing bleeding, symptoms of poor tissue oxygenation, or persistently low hematocrit values (20% to 25%) likewise should be transfused continuously. The target to which the hematocrit should be raised varies; in elderly patients it should be 30%, whereas in younger, otherwise healthy patients, hematocrit values in the 20% to 25% range may be satisfactory; in those with portal hypertension, it should not be above 27% to 28%. Packed red blood cells are preferred. Whole blood transfusions are reserved for the unusual patient with rapid, high-volume blood loss who cannot be cross-matched in a timely fashion. Fresh-frozen plasma or platelets or both should be administered to patients with defects in coagulation. Patients requiring greater than 10 units of packed red blood cells should receive fresh-frozen plasma or platelets or both. Warmed blood should be administered to patients requiring massive transfusions (i.e., >3000 mL). The hematocrit should be checked after each transfusion, but understanding that serial hematocrits are not a substitute for ongoing clinical assessment. When blood transfusion is deemed unnecessary, iron supplementation is indicated.

HISTORY, SYMPTOMS, AND SIGNS

The history helps the clinician assess the severity of bleeding and make a preliminary assessment of the site and cause. Age is an important component of the history. Elderly patients may bleed from a number of diseases less common in younger persons (i.e., diverticula, ischemic colitis, cancer), whereas bleeding in younger patients is more likely from ulcer disease, esophagitis, or varices. Bleeding in patients under 30 years of age may be due to Meckel's diverticula, which is rare in older patients. Known previous gastrointestinal disease or prior bleeding focuses the differential diagnosis immediately on bleeding from a similar source (e.g., hereditary hemorrhagic telangiectasia, ulcer disease, diverticular bleeding). A history of previous surgery broadens the differential diagnosis—e.g., previous aortic surgery and aortoenteric fistula. Known liver disease raises the possibility of bleeding associated with portal hypertension. Ingestion of aspirin or other nonsteroidal anti-inflammatory drugs makes bleeding from ulceration more likely. Other historical features important to ascertain include the presence of abdominal pain (peptic ulcer disease,

mesenteric or colonic ischemia), retching (Mallory-Weiss tear), or change in bowel habits, anorexia, or weight loss all of which point to malignancy. Elderly patients may be less likely to report abdominal pain associated with bleeding ulcers [6]. The history is also critical in ascertaining whether nongastrointestinal sources may be the cause of apparent gastrointestinal bleeding, especially from the nasopharynx.

Physical examination may reveal the presence of cutaneous signs (spider angiomata, Dupuytren's contractures) or other evidence of liver disease (splenomegaly, ascites, caput), that suggests the possibility of portal hypertension. Acanthosis nigricans may reflect underlying cancer (especially gastric cancer); cutaneous telangiectases of skin and/or mucous membranes and lips raise the possibility of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu); pigmented lip lesions are seen with Peutz-Jeghers syndrome; cutaneous tumors suggest neurofibromatosis; purpura is consistent with vascular disease (Henloch-Schönlein purpura or polyarteritis nodosa). Abdominal tenderness (peptic ulcer, pancreatitis, ischemia), abdominal masses, lymphadenopathy (malignancy), and splenomegaly (cirrhosis, splenic vein thrombosis) are all important to detect. It should be emphasized that gastrointestinal bleeding in the setting of anticoagulation therapy, even in patients taking warfarin and who have a supratherapeutic international normalized ratio (INR), is most often caused by underlying gastrointestinal tract pathology [7].

Hematemesis and *melena* are the most common symptoms and signs of gastrointestinal bleeding. Melena is caused by delivery of at least 50 mL of blood into the upper gastrointestinal tract, although volumes of up to 100 mL may be clinically silent [8]. Vomiting of bright red blood usually indicates significant upper gastrointestinal bleeding, often from varices or an arterial lesion [9]; however, small amounts of hematemesis are alarming. Therefore, careful inquiry about the volume of vomited blood is essential. Patients with coffee ground emesis are not usually bleeding actively but have had a recent or even remote bleed. Although hematochezia is due to bleeding from many sites in the gastrointestinal tract, bleeding is brisk and often hemodynamically significant when the source is the upper gastrointestinal tract. Chronic occult blood loss may lead to end-organ symptoms such as lightheadedness, dyspnea, angina pectoris, or even myocardial infarction.

Bedside examination of the character of the stool output provides critical information not only about the site of bleeding, but also about the acuity of bleeding. For example, patients with brown stools are unlikely to have aggressive bleeding. In contrast, patients who are actively passing stools containing red blood, maroon-colored blood, or melena—even in the absence of a positive nasogastric lavage—are likely to have active bleeding. Patients with infrequent stools are unlikely to be actively bleeding, and those with a history of coffee ground emesis only and normal-appearing stools, often positive for occult blood, have usually had a trivial bleed.

LABORATORY EVALUATION

The hematocrit value, when determined soon after the onset of bleeding, may not reflect blood loss accurately. Because equilibration with extravascular fluid and subsequent hemodilution requires several hours, a single hematocrit level may not reflect the degree of bleeding. Thus, the hematocrit is a poor predictor of hemodynamic stability. The hematocrit value falls as extravascular fluid enters the vascular space to restore volume, a process that is not complete for 24 to 72 hours [10] (Figure 1).

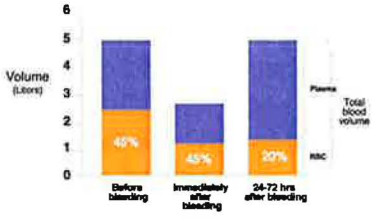

Figure 1. Hematocrit and blood volume. Plasma volumes (blue bars), red blood cell volumes (orange bars), and hematocrit values (%) before bleeding and after 2 L blood loss are shown.

The blood urea nitrogen (BUN) level may be mildly elevated in patients with upper GI bleeding. The elevation is typically out of proportion to elevation in the serum creatinine level [11], due to breakdown of blood proteins to urea by intestinal bacteria and its absorption, as well as from a mild reduction in glomerular filtration rate.

CLINICAL LOCALIZATION OF BLEEDING

The localization of bleeding begins with a careful history and physical examination. Hematemesis is from an upper gastrointestinal source of bleeding. Melena indicates that blood has been in the gastrointestinal tract for extended periods of time[10] and is usually the result of upper gastrointestinal bleeding, but its source may be the distal small bowel or even the ascending colon. In the latter instance, the volume of bleeding is too little to cause hematochezia but sufficiently large to provide hemoglobin for degradation. Approximately 10% of all patients with rapid bleeding from an upper source present with hematochezia [12].

The nasogastric lavage has been used extensively to help differentiate upper from lower gastrointestinal bleeding [13, 14]. A bloody aspirate confirms the upper gastrointestinal tract as the source of bleeding, since the false-positive rate is extremely low, and is usually due to nasogastric trauma [13]. It is important to emphasize that it may be extremely difficult to judge the acuity or activity of bleeding using nasogastric lavage; the correlation between the acuity of bleeding and the physician assessment of bleeding is weak, with a 79% sensitivity and 55% specificity for active bleeding [14]. Thus, use of the nasogastric lavage alone or as a primary tool to assess bleeding activity is discouraged. Assessment of vital signs and the use of bedside diagnostic criteria is the most effective means to determine bleeding activity. Further, a positive nasogastric lavage provides no information about the etiology of bleeding.

Although a nonbloody nasogastric aspirate suggests that bleeding is from a source other than the upper gastrointestinal tract, it is negative in up to 25% of patients with upper gastrointestinal bleeding. Even a bile-colored aspirate, which signifies sampling of the duodenum, does not exclude an upper gastrointestinal source of bleeding. If there is any question about the location of bleeding in a patient with hematochezia, especially in patients with hemodynamic instability, a nasogastric tube should be placed. Testing for occult blood in nasogastric aspirates, while commonly performed, is rarely necessary and helpful only when a coffee ground appearance of the aspirate may be caused by some foods. Although nasogastric tubes are useful to help determine the site of bleeding and to help direct further investigation, there is no evidence that their use affects the outcome.

Other clues to an upper gastrointestinal source of bleeding include hyperactive bowel sounds and an elevation in the BUN level out of proportion to creatinine [11].

DIAGNOSTIC TESTS

Diagnostic tests, of course, are important in the evaluation of patients with gastrointestinal bleeding. The major categories of tests available include: (1) endoscopy; (2) barium radiographs; (3) radionuclide imaging; (4) angiography; and (5) miscellaneous tests (abdominal computed tomography). Some help only in diagnosis; others possess therapeutic potential. Radiographic tests fall in the former category and endoscopy the latter. The importance of endoscopic therapy is emphasized by studies performed before the advent of endoscopic therapy, which demonstrated that endoscopy per se did not affect outcome for patients with upper gastrointestinal bleeding [15].

THERAPY

A major goal of treatment is to stop bleeding and prevent rebleeding. The major forms of therapy include (1) pharmacologic; (2) endoscopic; (3) angiographic; and (4) surgical. The use of each of these modalities has undergone tremendous change since the early 1980s and, in addition, each varies with the cause of bleeding. These therapeutic maneuvers are often complementary and require focused, multispecialty expertise. Treatment differs substantially among the different types of gastrointestinal bleeding.

III. Acute Non-Variceal Upper Gastrointestinal Bleeding

Upper gastrointestinal bleeding, which most commonly arises from mucosal erosive disease, has been estimated to account for up to 20,000 deaths annually in the United States. The overall incidence of acute upper gastrointestinal hemorrhage has been estimated at 50 to 100 per 100,000 patients per year, with an annual hospitalization rate of approximately 100 per 100,000 hospital admissions [4], the incident rate of upper gastrointestinal bleeding appears to be stable over recent years [4, 16-18]. The reason for this is likely to be multifactorial. On one hand, the introduction of proton pump inhibitors and efforts to eradicate *Helicobacter pylori* infection are likely to have reduced ulcer bleeding. On the other hand, the population is aging and is developing comorbid diseases that may predispose to upper gastrointestinal bleeding. Additionally, the use of aspirin and nonsteroidal anti-inflammatory agents appears to be leading to increased amounts of ulcer bleeding [19]. The risk of upper gastrointestinal bleeding appears to be increased in certain groups of patients, particularly those with underlying cardiovascular disease, chronic renal failure, and in patients over the age of 65 years [20, 21]. Peptic ulcer bleeding is predominantly a disease of the elderly – 68% of patients with peptic ulcer bleeding are over the age of 65, and 27% are over the age of 80 years [22].

PROGNOSIS

Many studies have addressed the factors that predict outcome in patients with upper gastrointestinal hemorrhage (see [9, 23] for review). Because upper gastrointestinal bleeding is most commonly caused by ulceration, prognostic factors for it tend to reflect those for bleeding peptic ulcer. Approximately 80% of upper gastrointestinal bleeding episodes are self-limited and require only supportive therapy [15, 24]. The two most important prognostic variables appear to be the cause of bleeding and the presence of underlying comorbidity. For example, patients with variceal hemorrhage have a mortality rate of at least 30% during their initial hospitalization, with a 1-year mortality rate approaching 60% [25]. A number of studies have identified clinical features of severe bleeding that can be recognized early in the patient's course, which predict recurrent bleeding and increased mortality (Table 2) [4, 17, 20, 26-32].

Poor Prognostic Signs in Acute Upper Gastrointestinal Bleeding

- Increasing age
- Increasing numbers of comorbid conditions (renal failure, liver failure, disseminated malignancy, heart failure, cardiovascular disease)
- Cause of bleeding (variceal bleeding > others)
- Shock or hypotension on presentation
- Red blood in the emesis and/or stool
- Increasing numbers of units of blood transfused
- Active bleeding at the time of endoscopy
- Bleeding from large (> 2.0 cm) ulcers
- Bleeding from a visible or spurting vessel
- Onset of bleeding in the hospital
- Emergency surgery
- Admitted on a weekend

Several scoring systems have been designed to identify patients with a high risk of adverse outcomes; the measures have generally been ascertained from mathematical models of risk of death or rebleeding and have been developed for upper and lower GI bleeding ([27, 33-38] and see [23] for review). Although such models are attractive conceptually, they have generally failed to gain popularity among practicing clinicians - probably because most clinicians are comfortable with upper gastrointestinal bleeding and recognize the value or commonly available prognostic variables such as those highlighted in Table 2. Models

have also been developed to assess whether patients presenting with acute upper gastrointestinal bleeding require more aggressive (i.e., hospitalized) management. For example, one study developed an abbreviated "fast-track" screening score based on simple clinical features [39]. Patients were classified as at low risk of needing intervention if, at presentation, all the following were true: BUN less than 6.5 mmol/L, hemoglobin concentration greater than 130 g/L for men and 120 g/L for women, systolic blood pressure greater than 100 mm Hg, and pulse rate less than 100. Although virtually all patients who required treatment (i.e., transfusion, endoscopy) failed to meet criteria for low risk - they had a low hemoglobin concentration, high BUN level, tachycardia, or relative systolic hypotension - this tool identified only 32% of the minor bleeds that would require no intervention [39]. A low specificity of this triage system and others like it makes the value of such scoring strategies problematic. Some of the clinical scoring systems have incorporated endoscopic criteria in an attempt to further improve patient management [23]. Finally, use of complementary clinical data such as the nasogastric aspirate has been used to try to predict high risk endoscopic lesion [40].

Approach to Diagnosis and Therapy

Following hemodynamic stabilization and thorough patient assessment, management shifts rapidly to a consideration of the cause of bleeding and the best approach to making the diagnosis. The specific lesions that cause upper gastrointestinal bleeding are shown in Table 3. Since history and physical examination, although clearly important, do not uncover the precise etiology of the bleeding, diagnostic tests are necessary.

Table 3. Causes of Acute Upper Gastrointestinal Bleeding

Common causes	Less frequent causes	Rare causes
Gastric ulcer	Dieulafoy's lesions	Esophageal ulcer
Duodenal ulcer	Vascular ectasia	Erosive duodenitis
Esophageal varices	Portal hypertensive gastropathy	Aortoenteric fistula
Gastritis	GAVE (watermelon stomach)	Hemobilia
Mallory-Weiss tear	Gastric varices	Pancreatic source
	Neoplasia	Crohn's disease
	Esophagitis	No lesion identified

The primary diagnostic modality for evaluation of upper gastrointestinal hemorrhage is currently esophagogastroduodenoscopy. Although barium radiography can diagnose many upper gastrointestinal tract lesions accurately, it does not offer the opportunity to provide therapy, and is not recommended in acute upper gastrointestinal bleeding. While endoscopy is the method of choice, considerable controversy remains about whether patients with hemodynamically trivial bleeding require this procedure.

Nonetheless, for patients with significant bleeding, the mainstay of treatment for their bleeding lesions is endoscopic therapy. Indeed, it is the major justification for esophagogastroduodenoscopy in those with hemodynamically significant acute upper gastrointestinal bleeding, since endoscopic therapy unquestionably improves prognosis.[41] For this reason, this group of patients should undergo esophagogastroduodenoscopy as soon as possible.

Not only is esophagogastroduodenoscopy important because it allows specific therapy, but the endoscopic appearance of certain lesions may help triage care, and thereby reduce costs of hospitalization. For example, early endoscopy performed in the emergency department safely assigned 46% of patients with nonvariceal upper GI bleeding to outpatient care, significantly reducing hospital stay [42]. Additionally, the endoscopic appearance of specific lesions appeared to facilitate identification of low risk patients that may be managed on an outpatient basis or discharged early [43]. It has also been postulated that "urgent" esophagogastroduodenoscopy would identify high risk lesions early, and thus reduce hospital stay [44].

It is important to emphasize that esophagogastroduodenoscopy should be performed only when it can be accomplished safely and effectively. Patients must be adequately resuscitated prior to endoscopy, and the airway must be protected during the procedure; intubation should be performed in the setting of aggressive bleeding or altered mental status. In actively bleeding patients or those with blood obscuring the endoscopic view, lavage with a large-bore orogastric tube should be performed. Erythromycin, which stimulates gastric motility, can be used to help clear the stomach of blood and has been shown to provide clearer endoscopic views if given prior to endoscopy [45]. Appropriate endoscopic equipment is required - a therapeutic videoendoscope is mandatory; further, thermal coagulation devices and injection material must be readily available. A recommended approach to upper gastrointestinal bleeding is shown in Figure 2.

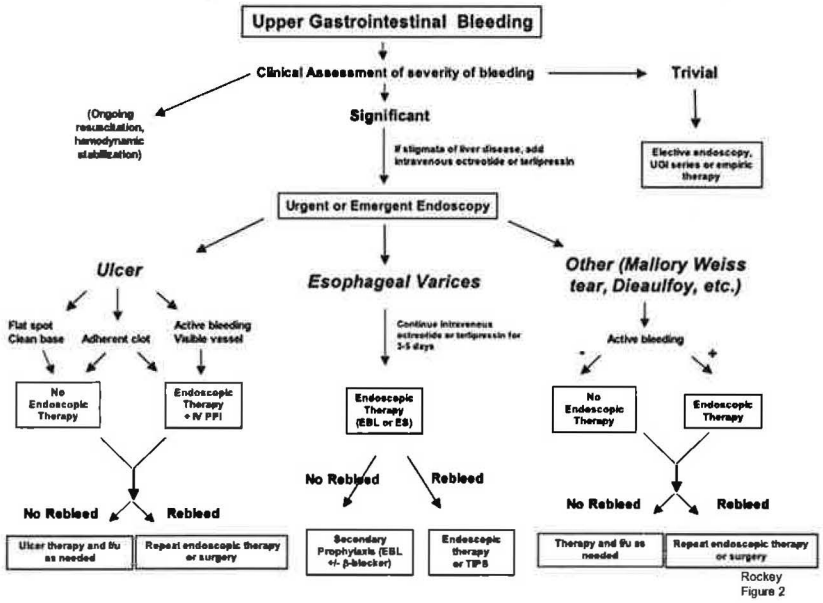

Figure 2. Algorithm for management of acute upper gastrointestinal (UGI) bleeding. Patients with significant hemodynamic compromise should be monitored and stabilized in an intensive care unit setting. Management of rebleeding is often complicated (see text for details). The management of adherent clots is controversial (see text for details). (TIPS, transjugular intrahepatic portosystemic shunt; EBL, endoscopic band ligation; ES, endoscopic sclerotherapy, IV PPI, intravenous proton pump inhibitor.)

Ulcer Bleeding - Predisposing Factors

A number of risk factors predispose to ulcer disease and its bleeding, the most prominent being acid, *Helicobacter pylori*, and nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and even SSRI's [18, 46-49]. In addition, underlying medical and clinical factors predispose to ulcer disease and bleeding. In a case control study of 1122 patients and 2231 controls [50] cardiovascular and cerebrovascular disease were independent predictors of peptic ulcer–related upper gastrointestinal bleeding. Chronic pulmonary disease and cirrhosis also are associated with peptic ulcer disease. Pharmacologic agents besides aspirin and NSAIDs may predispose to ulcer disease. Glucocorticoids historically have been associated with an increased risk of peptic ulcer, although newer data raise doubt about this association [51]. Alendronate has been linked to ~~the~~ development of gastric ulcers [52], although the incremental risk for development of upper gastrointestinal bleeding appears to be minimal [53]. Also, ethanol may potentiate the damaging effects of NSAIDs in the mucosa, and, as expected, anticoagulants will facilitate bleeding.

Hospitalization appears to be an important risk factor for development of ulcer bleeding (duodenal greater than gastric) [54]. Bleeding tends to occur after prolonged hospitalization and is most common in patients with severe comorbidities. Such "nosocomial" gastrointestinal bleeding is associated with poor outcome, and one study reported a mortality rate of 34% [54]. Nosocomial ulcer bleeders were less likely to have a history of previous ulcer disease (13% versus 50%; $P < 0.05$), to have *H. pylori* infection (14% versus 62%; $P < 0.0001$), or to be taking NSAIDs (48% versus 68%; $P = 0.08$) than those hospitalized for ulcer bleeding.

Anticoagulation increases the risk of bleeding from ulcer disease. The relative risk of hospitalization for bleeding ulcer in anticoagulated patients is about 3, and anticoagulants further increase the risk of bleeding in those taking NSAIDs [55]. Among users of oral anticoagulants, the adjusted incidence of hospitalization for bleeding peptic ulcer was 10.2 per 1000 person-years [55]. Compared with subjects who took neither anticoagulants nor NSAIDs, the relative risk of hemorrhagic peptic ulcer disease among users of both drugs was 12.7 (95% confidence interval, 6.3 to 25.7). The prevalence of NSAID use among anticoagulant users was 13.5%, similar to those not using anticoagulants. Such data emphasize the risk of anticoagulants, particularly for those who use NSAIDs.

Ulcer Bleeding - Prognostic Factors

Most ulcer bleeding is self-limited, and in these patients recovery is uneventful. However, a subset of patients have continued or recurrent bleeding, which is associated with a poorer prognosis. The prognostic factors emphasized in upper gastrointestinal bleeding (see Table 2) apply particularly to bleeding ulcers since they comprise the majority of upper gastrointestinal bleeding lesions. For example, old age, the presence of comorbid conditions, clinical evidence of aggressive bleeding, large ulcers (greater than 2 cm in diameter), and the onset of bleeding while hospitalized are important predictors of rebleeding and a poorer outcome.

The seminal observation of Griffiths and colleagues that a visible vessel in an ulcer base was predictive of uncontrolled or recurrent bleeding established the importance of the endoscopic appearance of ulcers [56]. The most critical endoscopic features in ulcer bleeding include the following stigmata of active/recent bleeding: active arterial spurting, oozing of blood, a visible vessel, and fresh or old blood clot (Table 4). Visible vessels are described endoscopically as elevated, dark red or purple lesions that protrude from the ulcer crater. A number of studies have examined endoscopic features as predictors not only of rebleeding but also of outcomes [57-59].

Table 4. Gastrointestinal Bleeding and Outcome From Peptic Ulcers Based on their Endoscopic Appearance

		Rebleeding		Surgery		Mortality	
Appearance	Frequency	No Rx	Rx	No Rx	Rx	No Rx	Rx
Active bleeding	18	55	20	35	7	11	<5
Visible vessel	17	43	15	34	6	11	<5
Adherent clot	15	22	5	10	2	7	<3
Flat spot	15	10	<1	6	<1	3	<1
Clean ulcer base	35	<1	-	0.5	-	2	-

Outcomes before and after endoscopic therapy are estimated based on available literature.
Adapted in part from: Laine and Peterson. Bleeding peptic ulcer. N Engl. J. Med. 331:717, 1994.

Ulcer Bleeding - Treatment

Because bleeding from gastroduodenal ulcers remains the most common and important form of upper gastrointestinal bleeding, treatment of this problem has been studied extensively. The goals of therapy are (1) to treat the peptic ulcer, and, thus, bleeding; (2) to stop active bleeding; and (3) to prevent rebleeding.

Endoscopic Therapy

Endoscopic treatment is widely accepted as the most effective method to control acute ulcer bleeding, and indeed, predicated on the appearance of the ulcer at the time of endoscopy, for prevention of ulcer rebleeding. Although individual studies are generally too small to show a significant effect of endoscopic therapy on mortality, meta-analysis demonstrated that endoscopic therapy prevents not only rebleeding but also death [41]. Experts and national gastroenterologic societies concur on the importance and effectiveness of

endoscopic therapy for patients with high-risk ulcers (Table 4) [60, 61]. As emphasized in this table, high-risk lesions identified at the time of endoscopy include actively bleeding lesions and ulcers with a non-bleeding visible vessel ("pigmented protuberance"); these lesions should be treated endoscopically. Management of ulcers with adherent clots is controversial. However, two small studies demonstrated that aggressive irrigation followed by endoscopic therapy (combined injection and thermal treatment) significantly reduced the likelihood of rebleeding [62, 63]. Flat, pigmented spots or lesions with slow oozing of blood no other stigmata do not appear to benefit from endoscopic therapy; decisions about whether to treat these should be individualized. Clean-based ulcers have a very low rate of rebleeding and generally should not be treated endoscopically.

Despite the data supporting the use of therapeutic endoscopy in ulcer bleeding, several important questions remain. First, lack of standardized definitions and lack of agreement about the various stigmata of recent hemorrhage [64] contribute to less than optimal understanding of the natural history of bleeding lesions. Second, therapeutic endoscopy can be dangerous, leading to further bleeding or perforation (up to 20% and 1% of patients, respectively). Finally, therapeutic endoscopy can add to the cost of treatment. Therapeutic endoscopy is clearly an important component of the management of patients with active bleeding or high-risk lesions, but it must be performed by experts in appropriate clinical settings. A number of endoscopic therapies are available (injection therapy, coagulation therapy, etc...) – and are essentially similar in effectiveness (Table 5).

Table 5. Endoscopic Therapies Used in Ulcer Bleeding

Injection
Saline
Water
Ethanol
Epinephrine*
Sclerosants
Fibrin glue
Thrombin
Thermal
Argon laser
Monopolar electrocoagulation
Bipolar or multipolar electrocoagulation*
Heater probe*
Hemoclips
Argon plasma coagulation
Band ligation
Endoloops

* Most common

Pharmacologic Therapy

Pharmacologic therapy for both peptic ulcer disease and bleeding has evolved enormously. A number of pharmacologic agents have been used to treat active ulcer bleeding: octreotide, somatostatin, vasopressin, secretin, H_2-receptor antagonists, proton pump inhibitors, antifibrinolytics, and prostaglandins. Although a few compounds have been marginally effective in stopping ulcer bleeding or preventing ulcer rebleeding, the only therapy for which sufficient evidence currently exists is the use of proton pump inhibitors. The greatest risk for rebleeding from ulcer disease is within the first 72 hours after the bleeding episode, so the benefit of pharmacologic therapy may be in either stopping acute bleeding or in preventing early rebleeding—most of the available literature fails to distinguish between these two events. Furthermore, most studies have examined proton pump inhibitors in the era of therapeutic endoscopy, so the effect of these agents must be considered additive to therapeutic endoscopy.

In contrast, proton pump inhibitors have significantly better acid-reducing characteristics, particularly at high doses, and they appear to be effective at preventing ulcer rebleeding in high-risk patients (Table 6) [65-70]. Although the designs of these studies contained a number of variables (e.g., definition of rebleeding, doses of drug used, extent of endoscopic therapy), the trend toward reduction in rebleeding is clear.

Table 6. Effectiveness of Omeprazole in Peptic Ulcer Rebleeding*

Study	N	Endoscopic Therapy	Bleeding rate		P Value
			Control	Omeprazole	
Hasselgren (1997)	322	†yes	26/163 (17%)	12/159 (8%)	N/S
Schaffalitzky de Muckadell (1997)	229	‡yes	37/118 (25%)	20/111 (18%)	N/S
Khuroo (1997)	220	no	40/110 (36%)	12/110 (11%)	<0.001
Lin (1998)	100	yes	I**8/50 (16%)	0/50 (0%)	0.01
Lau (2000)	240	yes	¹24/120 (23%)	5/120 (7%)	<0.001
Kaviani (2003)	149	yes	26/78 (33%)	12/71(17%)	0.02
Total	1111	-	151/639 (24%)	61/621 (10%)	-

* Only large studies are included, all studies examined patients with high risk lesions - actively bleeding ulcers, visible vessels and/or adherent clots. Omeprazole was given intravenously in the majority of studies.
†20/322 patients (all with spurting vessels) received endoscopic therapy at index endoscopy
‡ Approximately 76% of patients underwent endoscopy (with or without therapy) prior to omeprazole
¹ Bleeding at 3 days is shown
**The control group received intravenous cimetidine followed by oral cimetidine
N/S = not stated

Although the cell and molecular mechanism by which PPIs work remains unclear (the rationale for their use is presumably linked to improved

ulcer healing in a less acidic environment), when patients are treated with these agents, the rate of rebleeding is clearly reduced. Meta-analysis demonstrated that proton pump inhibitors are superior to H2-receptor antagonists and placebo in preventing rebleeding and the need for surgery in patients with ulcer bleeding, although they did not appear to reduce mortality [71]. The use of proton pump inhibitors appears to be cost effective in patients with ulcer bleeding; additionally proton pump inhibitors administered intravenously appear to be even more cost effective than those given orally [72-74]. Notwithstanding these data, a number of issues remain unresolved. For example, some studies used oral omeprazole (typically 40 to 80 mg every 12 hours), while others employed an intravenous route of administration (often a bolus of 80 mg, followed by infusion of 8 mg/hour). In the United States, not all proton pump inhibitors are approved for intravenous use. Thus, as of this writing, it is unknown which route of administration, which dose, or which agent is most effective. Further, it is unknown what the most appropriate duration of therapy is.

IV. Variceal Bleeding

Causes of Acute Upper GI Bleeding in Cirrhotics

Esophageal varices (EV)	41%
*EV + PHG	30%
Ulcer	11%
PHG only	9%
Dielafoy	2%
Gastritis/duodenitis	1%
Other	6%
Total	100%

(*Portal hypertensive gastropathy)

(From Trey Lyles et al - Parkland Memorial Hospital 2003-2005; n = 329)

The topic of portal hypertension and variceal bleeding merits its own grand rounds (coming some day soon!), and thus will be covered only briefly. First, it is important to recognize that patients with cirrhosis may bleed from lesions other than varices, including not only portal hypertensive gastropathy, but also ulcer disease and other lesions (Table 7). Thus, it is essential to first delineate the cause of bleeding. If portal hypertensive, the goals of therapy are to treat underlying portal hypertension to stop active bleeding, and to prevent rebleeding. Please see reference # 25 for a detailed review of esophageal variceal hemorrhage.

V. Acute Lower Gastrointestinal Bleeding

Acute lower gastrointestinal bleeding is distinct clinically from upper gastrointestinal hemorrhage in epidemiology, prognosis, management, and outcome. Lower gastrointestinal bleeding encompasses a wide clinical spectrum ranging from trivial hematochezia to massive hemorrhage with shock, requiring emergency hospitalization. Although most instances of lower gastrointestinal bleeding are self-limited and do not require hospitalized care, approximately 21 per 100,000 adults will require hospitalization per year for severe bleeding [3]. Hospitalization rates for lower gastrointestinal bleeding are approximately one third of those for upper gastrointestinal bleeding [34] and, in a survey by the American College of Gastroenterology, accounted for 24% of all bleeding events [75]. Although lower gastrointestinal bleeding is reportedly less common than upper gastrointestinal bleeding, it is certainly underreported, as evidenced by a cross-sectional survey of American population in which 14% experienced some amount of rectal bleeding during a 12-month period, but only a fraction sought medical care [76]. Notably, the incidence of lower gastrointestinal bleeding is higher in men and increases with age, presumably due to the high incidence of diverticulosis and vascular disease in this group.

Initial management of patients with lower gastrointestinal bleeding is similar to patients with acute upper gastrointestinal hemorrhage, including assessment of the severity of bleeding, hemodynamic stabilization, and determination of prognosis. Subsequently, the clinician's attention turns to consideration of the site, potential cause(s), and specific therapy of bleeding.

PROGNOSIS

The severity of lower gastrointestinal bleeding varies from very mild blood loss, usually manifest as intermittent hematochezia, to hemodynamically life-threatening bleeding. Compared with upper gastrointestinal hemorrhage, few data on prognostic variables for lower gastrointestinal bleeding exist. In one study that examined clinical predictors of the severity of lower gastrointestinal bleeding (severe bleeding was defined as transfusion of ≥ 2 units of blood and/or hematocrit decrease of ≥ 20%), it was demonstrated that the following clinical data were associated with severe bleeding: heart rate ≥ 100 beats/min (odds ratio [OR], 3.67; 95% confidence interval [CI], 1.78-7.57); systolic blood pressure, ≤ 115 mm Hg (OR, 3.45; 95% CI, 1.54-7.72); syncope (OR, 2.82; 95% CI, 1.06-7.46); nontender abdominal examination (OR, 2.43; 95% CI, 1.22-4.85); bleeding per rectum during the first 4 hours of evaluation (OR, 2.32; 95% CI, 1.28-4.20); aspirin use (OR, 2.07; 95% CI, 1.12-3.82); and more than 2 active comorbid conditions (OR, 1.93; 95% CI, 1.08-3.44) [35]. Thus, clinical variables that predict severity of bleeding have been identified in lower gastrointestinal bleeding that are similar to those identified in upper gastrointestinal bleeding although the acuity of hemorrhage in patients with lower gastrointestinal bleeding is usually less than in upper gastrointestinal hemorrhage. Orthostasis and shock were less common in patients with lower gastrointestinal hemorrhage than in those with upper gastrointestinal hemorrhage (19% vs. 35%, respectively) [75] and transfusion was more often required in upper gastrointestinal bleeders (64% vs. 36%, respectively). Nonetheless, about 50% of patients with lower gastrointestinal bleeding referred to an open-access endoscopy unit exhibited some form of hemodynamic disturbance, including 9% with cardiovascular collapse, 10% with syncope, and 30% with orthostasis [77].

APPROACH TO DIAGNOSIS AND THERAPY

Table 8. Causes of Acute Lower Gastrointestinal Bleeding

Common causes
Diverticula
Vascular ectasia
Less common causes
Neoplasia (including post polypectomy)
Inflammatory bowel disease
Colitis
Ischemic
Radiation
Unspecified (infectious or nonspecific)
Hemorrhoids
Small bowel source
Upper gastrointestinal source
No lesion identified
Rare causes
Dieulafoy's lesions
Colonic ulcerations
Rectal varices

Adapted from Schmulewitz and Rockey, GIE 2003.

As with upper bleeding, historical information gives clues. Lower gastrointestinal bleeding in elderly patients is commonly caused by colonic *diverticula* or *vascular ectasias*, whereas in young patients, infectious or inflammatory conditions are more likely [78, 79]. Such bleeding in other specific subsets of the population raises the possibility of other diagnoses—e.g., the most common cause of lower gastrointestinal bleeding in HIV-infected patients is cytomegalovirus (CMV) infection [80]. NSAIDs appear to be associated with lower gastrointestinal bleeding, especially from diverticula [81]. Bleeding from diverticula or vascular ectasias is often painless; hence, the presence of abdominal pain suggests that inflammatory or ischemic colitis is more likely. A history of radiation, previous surgery, particularly vascular surgery, constipation, change in bowel habit, and anorectal disease or trauma is important to consider in making a correct diagnosis. Causes of lower gastrointestinal hemorrhage are shown in Table 8.

The evaluation should rapidly progress to an understanding of the character of the stool output. Since accounts of hematochezia vary considerably, it is important that the color of the blood first seen by the patient be ascertained. Such information appears to be the most informative [82]. Bright red blood most commonly indicates a distal source or a rapidly bleeding proximal source, whereas black stool indicates a slowly bleeding right colonic or more proximal source. Accordingly, in patients with apparent massive lower gastrointestinal bleeding, it is important to exclude upper gastrointestinal hemorrhage by examining the aspirate from a nasogastric tube.

The diagnostic approach to lower gastrointestinal bleeding is controversial and not yet standardized. Some investigators recommend urgent anoscopy and flexible sigmoidoscopy for immediate evaluation of hematochezia. I strongly encourage anoscopy in most patients as part of the initial diagnostic evaluation (Figure 3). It is easily performed, inexpensive, and the best way to detect local anorectal abnormalities such as internal hemorrhoids, anal lacerations, tears, and fistulas. Flexible sigmoidoscopy may be diagnostic, following an enema preparation, for ulcerative or infectious colitis, hemorrhoids, proctitis, or solitary rectal ulcer, thus eliminating the need for emergency colonoscopy. However, this approach has not been widely studied, and sigmoidoscopy is rarely as informative as colonoscopy. Furthermore, the presence of an anal or rectal lesion does not exclude a more proximal bleeding lesion.

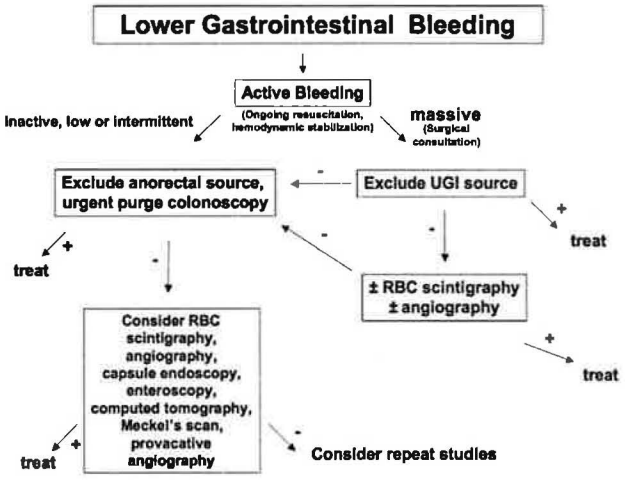

Figure 3. Algorithm for management of lower gastrointestinal bleeding. Recurrent bleeding is not addressed in the figure, but requires consideration of repeat studies, and in some patients, surgical intervention.

Few prospective data are available to judge the relative efficacy of the various diagnostic tests for lower gastrointestinal bleeding, including barium enema, colonoscopy, tagged red blood cell (RBC) scintigraphy, and visceral angiography. Barium enema is not recommended as part of the initial evaluation for acute lower gastrointestinal bleeding because it has a low diagnostic yield in this setting, and it may also interfere with subsequent performance of other tests, particularly endoscopy. RBC scintigraphy has been used extensively in patients with lower gastrointestinal hemorrhage but has no therapeutic capability. Colonoscopy, angiography, and surgery are all important diagnostic tools, and each has therapeutic potential.

Colonoscopy

Although use of early endoscopy for the diagnosis and treatment of upper gastrointestinal bleeding is predicated on sound data, early endoscopy for lower gastrointestinal bleeding has not been similarly adopted. Historically, colonoscopy has been used primarily for nonurgent investigation of patients with lower gastrointestinal bleeding, usually after cessation of bleeding and colonic preparation. The reluctance to perform colonoscopy acutely is due to poor visibility, potential for complications, and theoretical concern about the adverse effects of purging the colon in the setting of active gastrointestinal bleeding.

One clear advantage of colonoscopy is that it provides an avenue for early diagnosis, and thus may allow early triage. This possibility is supported by study demonstrating that the length of time from presentation to colonoscopy is an independent predictor of hospital length of stay [78, 83]. The shorter the time between presentation and colonoscopy, the shorter the length of stay. Further, given the broad spectrum of disorders causing lower gastrointestinal bleeding and the fact that few patients underwent therapy, the reduction in hospital length of stay seemed to be primarily related to improved diagnostic yield rather than therapeutic intervention.[83]

A number of reports show that urgent colonoscopy is safe and yields a specific diagnosis in a high proportion of patients in this setting (Table 9) [84-87]. The definition of "urgent" and the timing of procedures vary greatly both in clinical practice and in published reports. An additional consideration is that some studies have not differentiated a definitive from a presumptive diagnosis. The fact that only a small fraction of patients has undergone endoscopic therapy suggests that few definitive lesions have been identified, and that few have been treated. The advantages of urgent colonoscopy, i.e., performed as soon as the patient has been hospitalized and prepped, include the high likelihood of detecting an actively bleeding lesion or one with stigmata of bleeding, and thereby a lesion amenable to endoscopic therapy may be discovered. The largest randomized study performed to date revealed that while outcomes were not different, a diagnosis was made more frequently in those undergoing urgent colonoscopy (Table 10).

Table 9. Urgent colonoscopy for evaluation of lower gastrointestinal bleeding

Study	N	Bowel Preparation %	Specific Diagnosis N (%)	Endoscopic Therapy N (%)
Kok (1996)	190	85	148 (78)	10 (5)
Chaudry (1998)	85	0	82 (95)	17 (20)
Jensen (2000)	121	100	121 (100)	*10 (8)
Ohyama (2000)	345	100	307 (89)	48 (14)
Angtuaco (2000)	39	100	^26 (67)	4 (10)
Green (2005)	50	100	^48 (96)	17 (34)
Total	830	-	732 (88%)	106 (13%)

*Reported only patients who received therapy specifically for diverticular lesions
^A definite source of bleeding was found in 3 of 39 by Angtuaco et al, and 21 of 50 by Green et al.

Table 10. Definitive Bleeding Sites

Characteristic	Urgent	Standard
Diverticula	13	8
Vasc. Ectasia	4	0
Colitis	4	3
Total	*21	11

* P < 0.05 vs. standard

(Green B, Rockey DC, et al. AJG 2005.)

Some have proposed urgent, unprepared colonoscopy for evaluation of lower gastrointestinal bleeding. In one analysis of 85 consecutive patients who underwent 126 colonoscopies, a bleeding site was identified in 97% [85] Complications were uncommon; one patient developed asymptomatic free air after a cauterization procedure in the right colon, and two patients developed hyponatremia, possibly related to extensive irrigation of the colon.

Based on a high diagnostic yield, low rate of complications, and theoretical therapeutic potential, national gastroenterologic societies have concluded that colonoscopy is the diagnostic procedure of choice in most patients with lower gastrointestinal bleeding [88]. Whether it should be performed urgently with or without a purge preparation or can be performed expectantly is an open question at this time.

Tagged Red Blood Cell Scintigraphy

The use of scintigraphy, preferably with technetium-labeled RBC, in patients with lower gastrointestinal bleeding remains highly controversial. Although it may detect bleeding as small as 0.1 to 0.5 mL/min, the sensitivity can be decreased by bowel motility stimulated by intraluminal blood. Advantages of tagged RBC scintigraphy are (1) sensitivity to low rates of bleeding, (2) safety; (3) it is noninvasive; (4) no risk of contrast reaction, and (5) low cost. Potential disadvantages of scintigraphy include its lack of therapeutic capability and doubt about its accuracy.

Perhaps the most important question surrounding RBC scintigraphy is reliability in directing specific surgical treatment. In 635 positive scans reported in the literature, the site of bleeding was correctly localized by tagged RBC scintigraphy in 343 cases, confirmed by other tests in 269 (78%) [89]. One study assessing the reliability of RBC bleeding scans found that 8 of 19 (42%) patients who underwent surgery based only on a positive scan had recurrent bleeding [90]. Another study reported that of 18 patients operated on for lower gastrointestinal bleeding, 11 had negative scans for bleeding and the bleeding scan was

inaccurate in the other 7 patients; thus, in no instance did the scan direct the surgical intervention [91]. Based on these data, surgical therapy is not generally recommended on the basis of tagged RBC scintigraphy alone.

Specific Causes of Lower Gastrointestinal Bleeding

The two major causes of significant lower gastrointestinal bleeding are *colonic diverticula* and *vascular ectasia* (Table 8). Hemodynamically insignificant bleeding is frequently caused by hemorrhoids and neoplasia. Less common causes include solitary rectal ulcer, colonic varices, vasculitis, endometriosis, intussusception, and small intestinal lesions (small bowel tumors, small bowel ulceration, mesenteric vascular insufficiency, small bowel diverticula, Meckel's diverticulum, and aortoenteric fistula). Rare causes include drug-induced hemorrhagic colitis, portal colopathy, diversion colitis, and gastrointestinal bleeding in runners. The source of bleeding cannot be definitively identified in a significant number of patients [3, 78].

Treatment of Lower Gastrointestinal Bleeding

The majority of episodes of acute lower gastrointestinal bleeding cease spontaneously, regardless of source, but patients with continuing or recurrent bleeding require intervention. Therapy may be required to prevent rebleeding in patients at risk for serious complications of a recurrence. Therapeutic options are more limited than for upper gastrointestinal tract bleeding: endoscopic, angiographic, and surgical therapy. Currently, specific pharmacologic therapy for most patients with lower gastrointestinal bleeding is unavailable. Unfortunately, few data comparing the effectiveness of different therapeutic modalities are available at this time.

VI. Occult and Obscure Bleeding

Occult and obscure bleeding have been variously defined in the medical literature. For the purposes of this discussion, occult bleeding is taken to mean bleeding that is truly unknown to the patient and is typically manifest as fecal occult blood and iron deficiency anemia. In contrast, obscure bleeding is that which is apparent to the patient (typically manifest as hematemesis, melena, hematochezia), but in which the source cannot be identified by standard esophagogastroduodenoscopy and colonoscopy.

Occult Bleeding

Occult bleeding is by far the commonest form of gastrointestinal bleeding, afflicting at least 10% of the American population. True to the definition of occult, it is bleeding of which the patient is unaware, thus it is "hidden" or "concealed." The potential extent of such bleeding is emphasized by the observation that although instillation of 50 to 100 mL of blood into the stomach is required to produce melena consistently, patients losing 100 mL of blood per day may have grossly normal-appearing stools [92]. Thus, occult bleeding may be accurately detected only by testing for fecal blood, or by discovery of an iron deficiency anemia if bleeding has occurred over a sufficient time period. The term *occult bleeding* also implies that it is unexplained or mysterious; hence, from an obscure source. Evident bleeding from an unidentified source and site, though much less common than detection of occult blood in the stool or iron deficiency, stall is clinically challenging.

FECAL OCCULT BLOOD

Occult gastrointestinal blood loss is most commonly identified by simple detection of blood in the stool with standard fecal occult blood tests; when such tests have been examined in large populations, 2% to 16% of subjects have been reported to be ~~are~~ positive [93, 94]. Normal fecal blood loss varies from 0.5 to 1.5 mL per day [95, 96] and although most tests for fecal occult blood become positive when about 2 mL are lost per day, for consistent detection higher levels of fecal blood are required. Many tests are available; they are most commonly used to screen the colon for cancer [97, 98] (see also Chapter 115 for review of their use for colon cancer screening), reducing mortality from colon cancer [94, 99, 100]. The likelihood of detecting fecal blood depends not only on the sensitivity of a particular test but also the frequency and rate at which the causative lesion bleeds,[101] bowel motility, and the anatomic level of bleeding, all of which influence intraluminal metabolism of hemoglobin (Figure 4). Fecal occult blood tests clearly detect significant blood loss from many different lesions at many different locations in the gastrointestinal tract.

Fecal Occult Blood Tests

The prototypical fecal occult blood tests are based on the property of an organic compound, guaiac, to turn blue after oxidation by oxidants, peroxidases, or the pseudoperoxidase of hemoglobin in the presence of an oxygen donor such as hydrogen peroxide. Guaiac tests are more sensitive for detecting bleeding from the lower than upper gastrointestinal tract since hemoglobin and its pseudo-peroxidase are continuously degraded as they move down the gastrointestinal tract (see Figure 4). The sensitivity of the different guaiac-based tests varies. Of the two most commonly used tests in the United States, Hemoccult II and Hemoccult II SENSA (both from SmithKline Diagnostics, Palo Alto, CA), the latter is substantially more sensitive for detecting fecal heme.[102] This difference is important in screening for occult blood since increases in sensitivity result in reduced specificity.

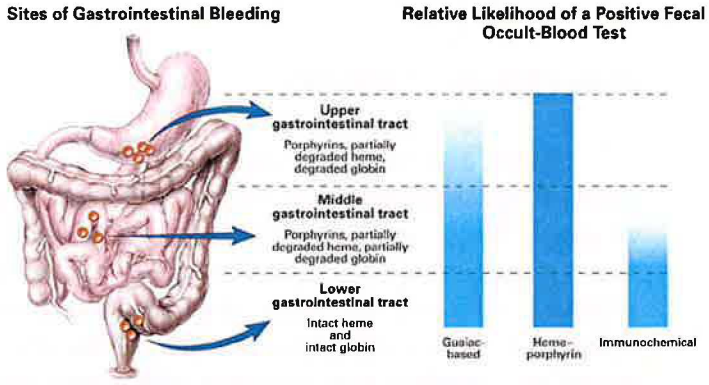

Figure 4. Sites of gastrointestinal bleeding, intraluminal metabolism of hemoglobin and detection of intraluminal blood by fecal occult blood tests. In the upper gastrointestinal tract, hemoglobin is cleaved to heme and globin by gastric pepsin or pancreatic proteases in the proximal small intestine. Some (generally <15%) intraluminal heme is reabsorbed in the small intestine. A portion of heme that is not absorbed is converted to porphyrins and iron through poorly understood mechanisms has been termed the intestinal converted fraction of heme. This fraction is not detected by guaiac tests but is detected by the heme-porphyrin assay (HemoQuant), which measures both heme and porphyrins, and is therefore a highly accurate indicator of bleeding, regardless of level. Globin in the upper gastrointestinal tract is digested by pepsin and pancreatic and intestinal proteases, and is thus not detected by immunochemical fecal occult blood tests. The biology of intraluminal hemoglobin degredation suggests that a combination of a guaiac-based test and an immunochemical test could theoretically help differentiate occult upper from lower gastrointestinal tract bleeding. (From Rockey DC: Occult gastrointestinal bleeding. N Engl J Med 341:38–46, 1999).

The likelihood that a guaiac test will detect fecal blood (heme) depends critically on the quantity of hemoglobin present in the stool. In turn, the amount of hemoglobin in the stool depends on the size and location of the bleeding lesion. Since distal (colonic) lesions are more likely to contain undegraded heme, guaiac-based tests are best at detecting more distal lesions. The amount of undegraded heme, however, will depend on variables such as stool transit time, extent of mixing, as well as degree of intraluminal degradation of heme by bacteria. The variation in the content of fecal hemoglobin has been highlighted; fecal hemoglobin levels must exceed 10 mg/g (10 mL daily blood loss) for 50% of Hemoccult II tests to be positive, yet stools with less than 1 mg/g of hemoglobin may be positive [103].

Immunochemical tests use antibodies directed against human globin epitopes to detect colonic blood and are highly sensitive (as little as 0.3 mL of blood added to stool can be detected), giving them a theoretical advantage in specificity over guaiac-based tests [104]. Although their specificity is better than guaiac-based tests, they do not detect small quantities of blood from upper gastrointestinal sources (see Figure 4) [104]. Their usefulness is limited by technical problems such as loss of hemoglobin antigenicity at room temperature and the requirement for laboratory processing. A variety of newer immunochemical test devices have helped circumvent these problems.

The heme-porphyrin test (HemoQuant, Mayo Medical Laboratories, Rochester, MN) measures porphyrin spectrofluorometrically and therefore allows precise determination of total stool hemoglobin. Substances that interfere with, or cause false-positive guaiac-based tests (e.g., vegetable peroxidases), do not affect this test. However, an important confounder of the heme-porphyrin assay is myoglobin, an important source of nonhuman heme found in red meats. This test is extremely sensitive for detecting occult blood loss, but its great sensitivity has limited its usefulness as a screening tool, primarily because of its high rate of false-positive tests.

IRON DEFICIENCY ANEMIA

Given the normal daily blood loss of 0.5 to 1.5 mL/day, a stool weight of 150 g, and circulating hemoglobin of 15 g/dL, the usual stool hemoglobin concentration is 0.5 to 1.5 mg/g of stool. Thus, under normal circumstances, a total of 0.25 to 0.75 mg of elemental iron is lost from gastrointestinal bleeding daily. A small amount of iron is also lost in sloughed intestinal cells and from minute amounts of bleeding, making the average daily iron loss approximately 1 mg (Figure 5). The absorptive capacity of the small intestine for iron can increase dramatically in response to iron depletion but normally is limited. Thus, iron deficiency results only when iron loss exceeds absorption, usually when blood loss exceeds 5 to 10 mL/day over many weeks.

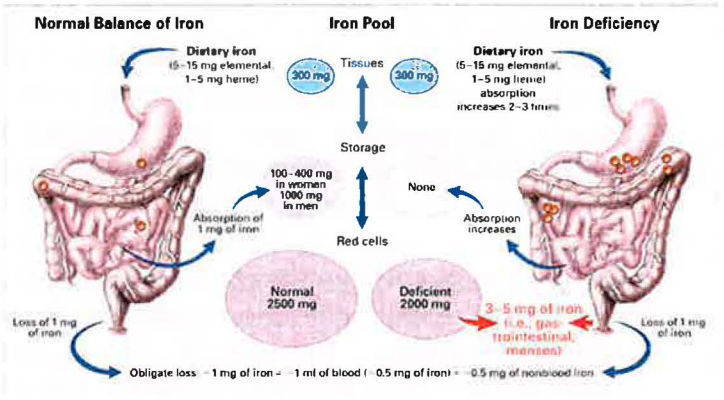

Figure 5. Gastrointestinal blood loss and iron balance. Normal obligate daily iron loss result from the following: (1) blood loss (presumably from gastrointestinal mucosal microerosions or microulcerations) and (2) iron in sloughed gut epithelial cells. Total daily iron loss is thus approximately 1 mg. The usual Western diet contains mostly elemental iron, of which about 10% is absorbed. Heme-iron derived primarily from myoglobin in meats is preferentially absorbed and accounts for 60% to 80% of the iron absorbed per day. Under normal circumstances, iron homeostasis is tightly regulated and daily iron loss is precisely balanced by iron absorption. Iron deficiency results only when the dynamic but limited, absorptive capacity of the small intestine is exceeded by iron loss. The time required to develop iron deficiency depends on the size of initial iron stores, the rate of bleeding and intestinal iron absorption. Iron deficiency generally occurs only with increased loss of over 5 mL of blood daily. Importantly, anemia is a late manifestation of the iron-depleted state. (From Rockey DC: occult gastrointestinal bleeding. N Engl J Med 341:38–46, 1999.

Iron deficiency anemia is the most common form of anemia worldwide. In the United States, 5% to 11% of women and 1% to 4% of men are iron deficient, and approximately 5% and 2%, respectively, have iron deficiency anemia [105]. Iron deficiency anemia is most commonly identified in women during their reproductive years because of menstrual and pregnancy-associated iron losses. In groups other than premenopausal women, iron deficiency anemia traditionally has been assumed to be the result of chronic occult gastrointestinal bleeding. Thus, the standard of care for men and postmenopausal women with iron deficiency anemia is to investigate for the presence of gastrointestinal tract pathology [92].

Approach to Evaluation and Differential Diagnosis – Fecal Occult Blood

In patients with occult bleeding the focus of the history and examination differ from that in patients with acute bleeding. Particular attention should be focused on anticoagulants and medications that can injure the gastrointestinal mucosa, including NSAIDs, alendronate, and potassium chloride. A family history suggesting a vascular anomaly (e.g., hereditary hemorrhagic telangiectasia) or a coagulopathy (e.g., von Willebrand's disease) is important. The physical examination should seek cutaneous abnormalities typical of systemic disorders that cause occult bleeding, such as dermatitis herpetiformis of celiac sprue, neurofibromas, café au lait spots, and axillary freckles of neurofibromatosis; the pigmented lip spots of the Peutz-Jeghers syndrome; osteomas and cysts of Gardner's syndrome; and the ectodermal (hair, nails) abnormalities of the Cronkite-Canada syndrome.

Lesions that bleed acutely may also bleed chronically. Therefore, virtually any gastrointestinal lesion can cause a positive fecal occult blood test (Table 11). The colon is the most common site of occult gastrointestinal blood due to the high prevalence of large colonic adenomatous polyps (i.e. greater than 1.5 cm) and adenocarcinoma. However, the upper gastrointestinal tract is also a frequent source of bleeding from gastroduodenal ulcers, vascular ectasias, esophagitis, and gastritis. Less common but important causes of occult bleeding include small intestinal tumors and ulcers, gastric adenocarcinomas, gastric vascular ectasia, and Cameron lesions.

Table 11. Differential Diagnosis of Occult Gastrointestinal Bleeding

Mass Lesions	Vascular
*Carcinoma (any site)	*Vascular ectasia (any site)
Large (> 1.5 cm) adenoma (any site)	Portal hypertensive gastropathy/colopathy
Inflammation	Watermelon stomach
*Erosive esophagitis	Hemangioma
*Ulcer (any site)	§Dieulafoy's ulcer
¶Cameron lesions	Infectious
Erosive gastritis	Hookworm
Celiac sprue	Whipworm
Ulcerative colitis	Strongyloidiasis
Crohn's disease	Ascariasis
Colitis (nonspecific)	Tuberculous enterocolitis
Idiopathic cecal ulcer	Amebiasis
Miscellaneous	Surreptitious
Long-distance running	Hemoptysis
Factitious	Oropharyngeal (including epistaxis)

Adapted from Rockey, DC. NEJM 341:38-46, 1999

The finding of occult blood in the stool requires investigation initially focused on the colon. Some controversy exists with regard to which colonic imaging test is the most appropriate modality [106]. Colonoscopy and air contrast barium enema are the most commonly used tools. Flexible sigmoidoscopy is thought to be required for patients undergoing air contrast barium enema to evaluate fully the rectosigmoid colon. Colonoscopy is generally regarded as the most accurate test and is the most widely used. Whereas some studies have demonstrated that air contrast barium enema accurately detects colonic malignancy and large adenomas, others report that it is significantly less accurate than colonoscopy [106, 107]. Nonetheless, it is important to realize that either test can miss serious neoplastic lesions [106-108].

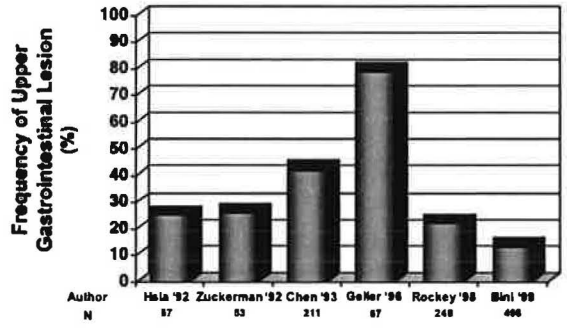

Figure 6. Frequency of upper gastrointestinal lesions in patients with fecal occult blood. In general, studies excluded patients with active bleeding. Variation in the criteria used to ascribe a specific lesion to the positive fecal occult blood test exists. The study by Geller and colleagues[1] included patients with small polyps detected in the colon.

The source of bleeding in patients with fecal blood and a normal colon may be in the upper gastrointestinal tract. Several studies have addressed this issue, reporting bleeding from potential upper gastrointestinal tract sites in proportion equal to or greater than the lower gastrointestinal tract (Figure 6) [1, 109-113]. Endoscopy of the upper gastrointestinal tract often leads to management changes in many cases. That patients with fecal occult blood have such a high number of upper gastrointestinal lesions is surprising since the guaiac-based

tests that were used in these reports were thought to have a relatively low sensitivity for detecting upper gastrointestinal blood; however, guaiac-based tests clearly are capable of detecting small amounts of upper gastrointestinal tract blood [102, 114]. Furthermore, many of the lesions identified in the upper gastrointestinal tract in these reports bleed sufficiently to produce positive guaiac-based tests [95, 102] Upper gastrointestinal tract malignancies were identified in each of these reports. An open question is whether it is cost-effective to proceed routinely with upper gastrointestinal tract investigation in patients with fecal occult blood and a normal colonic examination.

The appropriate evaluation for patients with occult blood found in stool obtained by digital rectal examination is controversial. Although anorectal trauma or dietary factors may lead to positive tests that may not reflect an underlying abnormality, nevertheless both symptomatic and asymptomatic patients with fecal blood detected by digital rectal examination harbor important lesions identified by gastrointestinal evaluation [112]. Available data indicate that the diagnostic yield for investigating occult blood detected by digital rectal examination is the same as for spontaneously passed stools [112, 115]. Thus, gastrointestinal tract evaluation is warranted for investigation of occult blood in the stool, and, if symptoms are present, should be directed accordingly. Whether testing stool obtained by digital rectal examination is a viable cancer screening option is currently unknown.

Occult gastrointestinal bleeding is often attributed to anticoagulant or aspirin therapy. However, fecal blood content in patients therapeutically anticoagulated have been normal [116, 117], and low-dose aspirin alone resulted in only minimally increased fecal blood. The combination of aspirin and warfarin caused still slightly higher amounts of fecal blood [116, 117]. Neither warfarin nor low-dose aspirin alone appears to cause positive guaiac-based fecal occult blood tests [117]. Thus, a positive fecal occult blood test should not be attributed to the effect of anticoagulation or aspirin alone, but rather should lead to investigation of the gastrointestinal tract. A prospective study in anticoagulated patients with positive guaiac-based fecal occult blood tests found that 15 of 16 patients had previously undiagnosed lesions, 20% of which were malignant [118].

Treatment of Patients with Fecal Occult Blood

Treatment of patients with fecal occult blood depends on the underlying disorder. Most bleeding mass lesions require surgical excision. NSAIDs should be withdrawn if possible, even if clear ulcer disease cannot be identified. Particularly difficult to treat are patients with vascular ectasias, which are often multiple and bleed chronically (discussed later). The prognosis of patients with positive fecal occult blood tests but no identifiable gastrointestinal pathology appears favorable but has not been rigorously studied. It appears that only a small proportion of such patients will develop obscure bleeding or iron deficiency anemia.

Approach to Evaluation and Differential Diagnosis – iron deficiency anemia

The approach is similar to that of patients with occult blood in the stool, with the exception that while investigation of the upper GI tract in patients with fecal occult blood may be considered controversial, it is mandatory in patients with iron deficiency anemia and negative colonic examination. History in patients with iron deficiency anemia is directed toward medications that can cause mucosal injury, symptoms of malignancy, or of other chronic diseases that may be associated with blood loss or failure to absorb iron. Again, cutaneous manifestations of gastrointestinal or systemic diseases may be present. In iron deficiency anemia, brittle, spoonlike nails suggest the presence of Plummer-Vinson syndrome.

Many lesions in the gastrointestinal tract can bleed chronically and lead to iron deficiency anemia (see Table 11). Although right-sided colonic cancers are considered the major source of occult bleeding and iron deficiency anemia, a variety of cross-sectional studies have documented prominent abnormalities in the upper gastrointestinal tract as the cause (Table 12). Indeed, in four series of 381 patients, upper gastrointestinal tract lesions believed to be consistent with chronic blood loss were identified more often than colonic [119-122]. Only 5% of patients had lesions capable of leading to iron deficiency in both upper and lower gastrointestinal sites.

Table 12. Iron Deficiency Anemia - Lesions

Test/Lesion	Percent*
EGD	
Esophagitis (severe)	18
Gastritis	15
Gastric Ulcer	11
Duodenal Ulcer	10
Gastric Cancer	7
Colonoscopy	
Colon Cancer	13
Large Adenoma (> 1.5cm)	8
Vascular Ectasia	5

* Percent of lesions detected in 381 patients. Pooled from Cook - IBM, Memphis - Cut, Rockey - NEJM and Kepczyk - DDS

Gastrointestinal tract evaluation of iron deficiency anemia

The colon has been emphasized in most iron deficiency anemia evaluation schemes. This is highly appropriate, particularly in elderly patients who have an increased risk of colorectal cancer. However, the upper gastrointestinal tract and small bowel must also be considered. In evaluating the gastrointestinal tract, and in particular the upper gastrointestinal tract for iron deficiency anemia, it is important to appropriately attribute the anemia to lesions likely to cause significant bleeding. Clearly, mass lesions and large ulcerative upper gastrointestinal lesions lead to significant blood loss and iron deficiency (Figure 7) [95] but trivial lesions such as mild inflammation and especially small adenomas do not. This point was emphasized by work that demonstrated that although 67% of patients with iron deficiency anemia had gastrointestinal tract lesions, fewer than one third of these patients had elevated hemoglobin levels in gastrointestinal lavage specimens [123]. This finding may have been due to daily variability in gastrointestinal bleeding, making one-time gastrointestinal blood measurement unreliable, but, nonetheless, the data suggest that it is unlikely that every lesion identified is associated with occult bleeding and iron deficiency.

Figure 7. A large ulcer in a patient with iron deficiency

Some clinicians believe that gastrointestinal symptoms in patients with iron deficiency anemia help direct the gastrointestinal tract evaluation,[121, 124, 125] whereas others have found symptoms to be unhelpful in localizing pathology [120, 122]. Notwithstanding, directed gastrointestinal tract evaluation is desirable to minimize both risk and cost. Although many patients are entirely asymptomatic, some patients with gastrointestinal lesions will have symptoms characteristic of common diseases, such as change in bowel habit (colon cancer) or epigastric pain (peptic ulcer). It is my belief that the initial investigation should be directed toward the location of specific symptoms (Figure 8). Since dual lesions are rare, identification of an abnormality consistent with bleeding, such as a mass lesion, large ulceration, or severe inflammation that is a likely cause of the

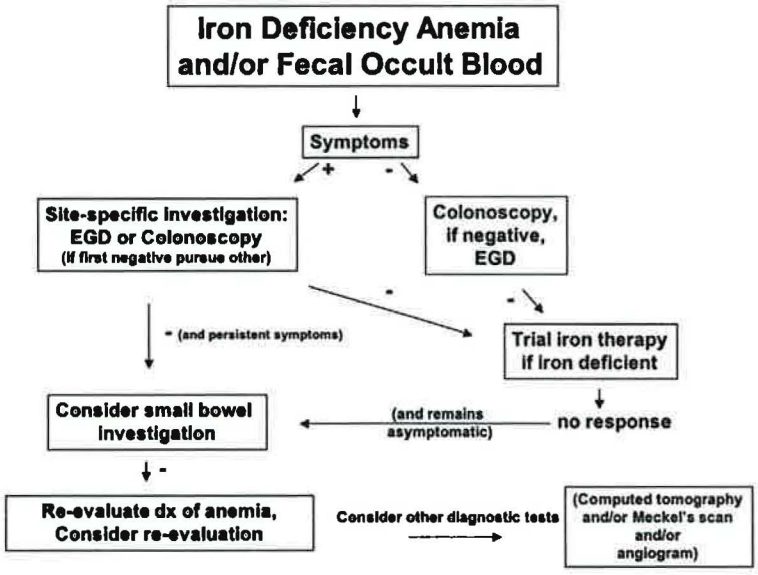

Figure 8. Algorithm for management of occult gastrointestinal bleeding (fecal occult blood and iron deficiency anemia).

symptoms, makes further evaluation unnecessary. In the absence of symptoms, particularly in elderly patients, evaluation should begin with the colon; if this examination is negative, the upper gastrointestinal tract should then be investigated.

Gastrointestinal evaluation of iron deficiency anemia in premenopausal women is controversial since it is extremely common in this population, affecting over 3 million women in the United States. A recent study found that 12% of premenopausal women with iron deficiency anemia had significant gastrointestinal tract abnormalities, half of which were malignant [124]. Moreover, lesions are frequently identified in the upper gastrointestinal tract, including large ulcers and malignancy [124, 126]. The available data suggest that gastrointestinal investigation for most premenopausal women with iron deficiency anemia is not only warranted, but that it should be individualized. Certainly those with gastrointestinal symptoms, weight loss, fecal occult blood, or severe anemia must be evaluated. Gastrointestinal tract evaluation is appropriate in asymptomatic women or those with abnormal menses whose menstrual blood loss appears to be inconsistent with the severity of their iron deficiency anemia.

The principal techniques to evaluate patients with iron deficiency anemia are endoscopic (esophagogastroduodenoscopy and colonoscopy) and radiographic (air contrast barium enema and upper gastrointestinal series). Radiographic studies are generally effective for detecting masses and large ulcerating lesions, but their sensitivity for vascular ectasias and more subtle mucosal lesions such as gastritis, esophagitis, and colitis is less than with endoscopic procedures. Since patients with iron deficiency anemia have a high pretest probability of disease, much of which is mucosal, or will require biopsy, endoscopic investigation is the best first choice since many patients would require endoscopy after radiographic studies. Both lower and upper endoscopy should be performed sequentially under the same conscious sedation, a sequence that is not possible if barium studies have preceded it. The cost-effectiveness of radiographic versus endoscopic studies requires further study.

Evaluation of the small bowel in iron deficiency anemia

The small bowel remains the potential site of bleeding in patients with negative examinations of the colon and upper gastrointestinal tract. Although tumors and vascular anomalies are the more common causes, mucosal disease must also be considered. Celiac sprue, a classic small bowel disease, not only leads to malabsorption of iron but also occult bleeding [127]. Also, mucosal ulcerative diseases of the small bowel should be considered in the differential diagnosis (radiographic examination by enteroclysis or small bowel follow-through is of limited value for detection of small bowel mucosal disease Enteroscopy of the small intestine is more sensitive for detecting mucosal abnormalities and small mass lesions and is preferred in patients with negative lower and upper gastrointestinal tract evaluations. Indeed, recent studies of enteroscopy in patients with iron deficiency anemia have identified abnormalities in 6% to 27% of patients [128]. Although such reports confirm that enteroscopy yields diagnoses of the source of occult bleeding and iron deficiency anemia, more investigation is required to define its role in the initial evaluation of iron deficient patients.

A major advance in small bowel investigation, an endoscopic capsule, has recently become available [129, 130]. The original capsule (made by Given Imaging, Yoqneam, Israel), 11 by 26 mm in size, contains four light emitting diodes, a lens, a camera, two batteries, and a radiofrequency transmitter (Figure 9). The capsule is capable of obtaining 2 images per second, while transmitting this data to a recording device worn by the patient. The data are subsequently downloaded to a computer workstation loaded with software that allows images to be analyzed. The capsule is disposable and because of its small size passes through the

gastrointestinal tract naturally. Patients typically undergo preparation to clear the gastrointestinal tract.

Figure 9. Capsule used in capsule endoscopy.

Given that the small bowel is difficult to visualize endoscopically, the technology promised by capsule endoscopy is extremely attractive [130]. Capsule endoscopy has been utilized in patients with iron deficiency anemia and has been demonstrated to identify the full gamut of important small bowel lesions [131, 132]. While such results are exciting, a major disadvantage of capsule endoscopy is its inability to administer therapy. At this date, outcome data for capsule endoscopy in patients with iron deficiency anemia is lacking [133-136]. It is clear that further studies are required to determine how capsule endoscopy should be used in patients with iron deficiency anemia.

Many patients with iron deficiency anemia will have no identifiable gastrointestinal tract abnormality after evaluation. If such patients are refractory to empiric iron supplementation, other tests should be considered, including angiography or computed tomography. If diagnostic evaluation is unable to elucidate a gastrointestinal abnormality, explanations for iron deficiency anemia should be considered, including non-gastrointestinal blood loss, misdiagnosis of the type of anemia, missed lesions, malabsorptive diseases, or nutritional deficiency.

Treatment of Iron Deficiency Anemia

When the diagnosis of iron deficiency anemia is established, iron therapy should be instituted. Oral ferrous sulfate, 325 mg two to three times daily, is recommended; it is inexpensive and effective. For those who are intolerant to ferrous sulfate, ferrous gluconate or fumarate are acceptable alternatives. Parenteral iron therapy is used only for patients with severe malabsorption or intolerance to iron supplements. The response of patients with lesions amenable to medical therapy, such as duodenal ulcer, esophagitis, and adenoma, to iron repletion is excellent. Most patients with unidentifiable gastrointestinal abnormalities generally respond to long-term iron therapy [121, 137]. If patients do not respond to iron therapy, the diagnosis of iron deficiency anemia should be reassessed and repeat gastrointestinal investigation should be contemplated. Re-examination of the colon for vascular ectasias, the esophagus for Cameron lesions within hiatus hernia, the stomach for atrophic gastritis, and the small bowel for vascular ectasias or celiac sprue can be helpful. The importance of re-examination of the gastrointestinal tract is emphasized by the finding that a bleeding source is within reach of the standard upper endoscope in up to 35% of such patients [128].

GASTROINTESTINAL BLEEDING OF OBSCURE ORIGIN

The source of bleeding cannot be identified in about 5% of patients with gastrointestinal bleeding [138, 139]. Whether an obscure site of bleeding may be clinically evident by obvious signs or symptoms or its occult nature is manifest only as refractory iron deficiency anemia, the diagnostic challenge is great, for readily identifiable causes of gastrointestinal bleeding have already been excluded by esophagogastroduodenoscopy and colonoscopy. Both continuing and recurrent gross or occult bleeding of unknown origin demands focus on the possible etiology and site of hemorrhage source, for only then can appropriate therapy be instituted.

Table 13. Causes of Obscure Gastrointestinal Bleeding

*Vascular ectasias
Small bowel neoplastic lesions
Hemosuccus panreaticus
Hemobilia
Aortoenteric fistula
Dieulafoy's ulcer (stomach > other sites)
Meckel's diverticulum
Extra-esohpageal varices (gastric, small bowel, colonic)
Diverticula (especially small intestinal)

Approach to Evaluation and Differential Diagnosis

Localizing the site, upper or lower, may be helped by a thorough history and physical examination. Although melena and hematochezia are usually associated with upper and lower gastrointestinal tract bleeding, respectively, patients with slow oozing from the distal small bowel or cecum may have melena and patients with aggressive bleeding from an upper gastrointestinal source may present with hematochezia. History and physical examination should focus particularly on symptoms and signs of diseases likely to be overlooked, including those reflecting small bowel disease (Table 13).

Repeat endoscopy in patients with obscure bleeding should be directed at the most likely site of bleeding (Figure 10), and ideally, if performed during active bleeding, a specific diagnosis may be made. In upper gastrointestinal bleeders, re-examination with a standard upper endoscope and/or enteroscope by an experienced operator will identify lesions in a substantial proportion of patients [128].

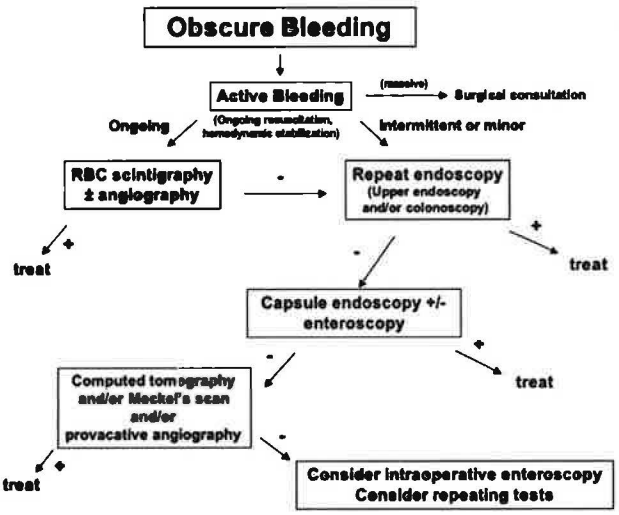

Figure 10. Algorithm for management of obscure gastrointestinal bleeding. Patients with recurrent bleeding should undergo repeat testing as deemed to be appropriate based on specific clinical features.

If a lesion cannot be identified at endoscopy, further evaluation depends on the briskness of bleeding. In those with active bleeding, technetium-99 radionuclide scanning or angiography should be performed. Technetium scanning is useful only to confirm the site of bleeding, and data assessing its impact on management in patients with obscure gastrointestinal bleeding are limited. Mesenteric angiography is less sensitive than technetium-99 radionuclide scanning but reportedly more often identifies a site of bleeding [140], perhaps because of selection bias in published studies. Other diagnostic tests such as computed tomography or Meckel's scan may be helpful in some patients.

In patients with subacute or intermittent bleeding in whom repeat endoscopy of the upper or lower gastrointestinal tract is negative, the focus of investigation should be broadened to include the small intestine. The lesions most commonly identified as bleeding sites in the small bowel include tumors and vascular ectasias, which vary in frequency depending on age. In patients between 30 and 50 years of age, tumors are the most common abnormalities, whereas in patients less than 25 years of age, Meckel's diverticula are the most common source of small bowel bleeding. Vascular ectasias predominate in older patients [141].

Small bowel examination can be accomplished with standard small bowel follow-through, enteroclysis, push enteroscopy, sonde enteroscopy, or intraoperative enteroscopy. Small bowel follow-through usually is inadequate to evaluate the small intestine. Enteroclysis is capable of detecting mass lesions of the small intestine but fails to detect many mucosal lesions, particularly vascular ectasias. Since vascular ectasias are often a major concern in this patient population, enteroclysis is probably best reserved for those in whom the suspicion of a mass lesion or small bowel diverticula is high or for those who have persistent bleeding and negative-push enteroscopy.

Enteroscopy in obscure bleeding

Enteroscopy in patients with obscure GI bleeding is undergoing a rapid evolution. Classic, "push", enteroscopy is rapidly being replaced by specialized types of enteroscopy such as "double" or "single balloon" enteroscopy. Sonde enteroscopy has been abandoned. Push enteroscopy consists of peroral insertion of a specialized, long, flexible endoscope or sometimes a standard pediatric colonoscope, and it should be performed in obscure bleeders. With the patient under conscious sedation, this instrument can be passed 50 to 60 cm beyond the ligament of Treitz, allowing expeditious and thorough examination of the distal duodenum and proximal jejunum. It identifies a source in 24% to 75% of patients with obscure bleeding [141-143]. The major advantages of push enteroscopy are that it is readily available, relatively safe, and both biopsy and endoscopic therapy can be performed. Double-balloon enteroscopy, which involves use of an endoscope and overtube are equipped with latex soft balloons, which can be inflated or deflated while performing the procedure [144]. Balloons are used to grip the intestine while inserting an endoscope (balloon pressure is low and thus safe and minimizes discomfort. By inflating the overtube balloon enough to grip the intestinal wall, the endoscope can be inserted further without forming redundant loops in the small intestine, and then the overtube can in turn be inserted while the endoscope balloon is inflated. This allows evaluation of the entire small bowel, with the added benefits of standard enteroscopy (biopsy and therapy). Other forms of enteroscopy are now becoming available, including "spiral" enteroscopy, and single balloon enteroscopy [145-148].

Capsule endoscopy in obscure bleeding

As emphasized above, capsule endoscopy offers the potential to non-invasively examine the intestinal tract. Since most true obscure bleeding originates in the small intestine, the introduction of capsule endoscopy has revolutionized the approach in these patients [130]. Currently, considering all factors, capsule endoscopy appears to be a highly attractive tool with which to evaluate the small bowel.

Capsule endoscopy has been examined in patients with obscure bleeding in cohort and observational studies [131, 135, 149-155]. In general, these studies demonstrate that the likelihood of identifying a potentially important lesion (i.e., "diagnostic yield") by capsule endoscopy is greater than enteroscopy, and in some series approaches 90%. However, despite these impressive results, definitive outcome data are lacking and future investigation in this area is required.

TREATMENT OF OBSCURE BLEEDING

Treatment of lesions that bleed in an obscure fashion is aimed at the underlying abnormality. Thus, mass lesions are usually resected. Endoscopic or surgical therapy is often successful in patients with large, focal vascular ectasias but may not be effective when vascular ectasias are multiple, as is often the case. For diffuse ectasias, pharmacologic therapy with estrogen/progesterone compounds [156, 157] has been tried, based on their amplification of clotting by an unknown mechanism. In a prospective longitudinal observational study of 43 patients with proven or presumed vascular ectasias treated with Ortho-Novum 1/50, containing 1 mg of norethindrone and 0.05 mg of mestranol (one tablet twice daily) [157] and followed for a mean time of 535 days (range, 25 to 1551 days), none of the 38 patients who were treated with combination hormonal therapy rebled, but the 5 patients who received estrogen alone had rebleeding episodes. Although side effects were reported as mild, other investigators have reported breast tenderness and vaginal bleeding in women and gynecomastia and loss of libido in men, necessitating cessation of therapy in a

significant proportion of patients [158]. Furthermore, controlled trials using estrogen/progesterone compounds have failed to show an advantage over placebo [158, 159].

Octreotide has also been tried in patients with bleeding due to diffuse vascular ectasia. At a dose of 0.05 to 1 mg subcutaneously per day, this compound was reported to be effective and without side effects [160]; however, no satisfactory controlled study has been done. Other agents, including aminocaproic acid, tranexamic acid, and danazol have been demonstrated in case reports to effectively control bleeding but, again, controlled data are lacking.

The role of therapeutic endoscopy in patients with obscure bleeding, particularly those with vascular ectasias, also remains controversial. Enteroscopic cauterization of vascular ectasias led to an improvement in hemoglobin and a reduction in blood transfusion requirements in some studies [161, 162] but not in others [157].

Results with intraoperative enteroscopy are also inconsistent. These procedures often identify a source of bleeding, but surgical resection of these lesions does not always prevent recurrent bleeding. Although some investigators have reported rebleeding rates of as low as 20% [163], the rebleed rate in other studies has been substantial [139], suggesting that caution is required with this approach. Importantly, intraoperative enteroscopy and possible resection require an experienced, skilled, and dedicated team.

Summary of Occult and Obscure Gastrointestinal Bleeding

Occult gastrointestinal bleeding is the most common form of gastrointestinal bleeding and most often is manifest as occult blood in the stool. Occult gastrointestinal bleeding may also be manifest as iron deficiency anemia, often the result of chronic undetected gastrointestinal bleeding. The approach to evaluation of patients with fecal occult blood and iron deficiency anemia is similar and usually begins with investigation of the colon. Colonoscopy is preferred but CTC or ACBE (+/-flexible sigmoidoscopy) may be an acceptable alternative. If evaluation of the colon does not reveal a bleeding site, evaluation of the upper gastrointestinal tract should be considered in all patients; in those with iron deficiency anemia, upper gastrointestinal examination is required. The role of small intestinal investigation is controversial; it is probably best reserved for patients with iron deficiency anemia and persistent gastrointestinal symptoms or those who fail to respond to appropriate therapy. The best test to examine the small intestine in patients with iron deficiency anemia remains unknown, although capsule endoscopy has gained considerable attention. Celiac sprue and other malabsorptive diseases must also be considered as a potential cause of iron deficiency anemia. The treatment and prognosis of patients with occult blood in the stool or iron deficiency anemia or both depends on the gastrointestinal tract abnormality(ies) identified. Those without identifiable bleeding sites generally respond to conservative management and have a favorable prognosis.

Patients with refractory iron deficiency anemia or clinically apparent but obscure bleeding make up a small fraction of all patients with gastrointestinal bleeding but represent perhaps the greatest diagnostic and therapeutic challenge in the realm of gastrointestinal bleeding. These patients should undergo aggressive endoscopic evaluation. Once upper and lower gastrointestinal tract lesions have been excluded as the source of bleeding, investigation should focus on the small bowel. The best test to evaluate the small bowel appears to be capsule endoscopy, and this test does not allow therapy, and enteroclysis and enteroscopy remain important options. In certain circumstances, other diagnostic studies are indicated (angiography, computed tomographic examination). The role of capsule endoscopy is evolving in this population, but these patients should probably undergo this test. Importantly,

the use of specific diagnostic tests is best governed by specific clinical scenario, test availability, and local expertise. Multiple small intestinal vascular ectasias usually cause bleeding in this subgroup of patients. Management of these patients is extremely difficult, requiring a focused and experienced team approach.

VII. Gastrointestinal Bleeding at Parkland Memorial Hospital

It has been well recognized that gastrointestinal bleeding is a common clinical event among inpatients at Parkland Memorial Hospital (PMH). Given the impressive volume of patients admitted at Parkland with this diagnosis, along with the interests of a number of faculty members at UTSW, we decided to develop a dedicated and team approach to management of patients with this disease, in particular focused on patients with upper gastrointestinal bleeding. Known as the "gastrointestinal bleeding team", the objectives of this team concept include the following:

1. To standardize the care of patients with gastrointestinal bleeding at PMH
2. To improve outcomes of patients with gastrointestinal bleeding at PMH
3. To perform discovery research in the field of GI bleeding that will lead to improvements in quality of care, and ultimately in novel management approaches for patients with gastrointestinal bleeding

Many of the key elements required to be effective have been in place (or were rapidly put in place), including the following: An optimized (for GI bleeding) mobile bleeding cart, appropriate endoscopic equipment, ability to perform emergent/urgent endoscopy (including in the ICU and even in the E.R.), ability to have nursing/ancillary support for emergent cases, dedicated patient care coordinator, a registry, a database, and a critical mass of skilled fellows and faculty.

Currently, there are a total of 16 protocols on the topic of GI bleeding ongoing at Parkland. Another half-dozen are in preparation or have been submitted. Over the last two years, 10 abstracts on the topic of GI bleeding have been submitted to the national GI meeting (DDW) for presentation, and multiple manuscripts are in preparation.

Active studies at PMH

Title	Lead Investigator
A prospective study using epinephrine injection with either an endoscopic hemoclip or a heater probe for bleeding from peptic ulcer disease	Luis Lara
Diagnostic and therapeutic upper endoscopy in anticoagulated patients with acute gastrointestinal hemorrhage	Luis Lara
Outcome after variceal bleeding - development of a risk score model	Trey Lyles
Endoscopy is safe in patients with upper gastrointestinal hemorrhage and low hematocrit	Valeska Balderas
Malabsorption as a cause of iron deficiency anemia (MC-IDA)	Natalie Bachir
The duration of octreotide study. An assessment of the duration of continuous intravenous octreotide in patients with portal hypertension and esophageal variceal hemorrhage	Don Rockey
Occult gastrointestinal bleeding caused by portal hypertensive gastropathy in patients with cirrhosis	Chris Cano
Occult gastrointestinal bleeding in cirrhosis	Chris Cano
The role of routine placement of nasogastric tube in patients with suspected upper gastrointestinal tract hemorrhage	Silvio Melo

Impact of a structured approach to the management of acute gastrointestinal bleeding in hospitalized patients	Sangeetha Duraiswamy
The clinical syndrome of a falling hematocrit without an obvious source of GI bleeding	Bryan Ong
Predicting the cause of upper gastrointestinal hemorrhage: does clinical experience matter?	Silvio Melo
Predicting the need for endoscopic therapy in patients with upper gastrointestinal hemorrhage using clinical features	Silvio Melo
Comparison of endoscopic hemostasis management preferences for nonvariceal GI hemorrhage among trainees and faculty members	Luis Lara
The role of narrow band imaging in the detection of early esophageal varices. Does the NBI grade varix exist? Interobserver agreement using narrow band imaging and white light	Luis Lara
Localization, efficacy of therapy, and outcomes of Dieulafoy lesions of the GI tract - the UT Southwestern GI Bleed Team experience	Luis Lara
Trends in epidemiology and therapy of upper gastrointestinal hemorrhage from gastroduodenal ulcer disease - the UT Southwestern GI Bleed Team experience	Luis Lara

It is expected that organization and standardization of care for patients with gastrointestinal bleeding at PMH, along with the implementation of a number of study protocols will lead to substantial new knowledge in the way gastrointestinal bleeding is managed. As well, it is expected that we will help establish national management guidelines and improve quality of care.

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