Acute Gastrointestinal Bleeding

Diagnosis and Treatment

Edited by

Karen E. Kim, MD

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Acute Gastrointestinal Bleeding

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Dedication

This book is dedicated to the memory of my mother, Sung-Ok Hong.

K.E.K.

PREFACE

Gastrointestinal (GI) bleeding is an extremely common clinical problem resulting in more than 300,000 hospitalizations annually in the United States. The overall incidence of upper GI bleeding is approximately 125 hospitalizations for every 100,000 people, with a male to female ratio of 2/1. Lower GI bleeding is far less common. Interestingly, the mortality from upper GI bleeding has remained stable at 10% over the past 45 years, despite improved diagnosis and newer therapeutic modalities, although this may reflect, at least in part, the aging population with a significantly higher GI bleeding mortality. Fortunately, the mortality from lower GI bleeding has decreased dramatically, despite the higher risk among the aging population owing, in large part, to early detection and intervention. Although GI bleeding can be acute or chronic, mortality from acute GI bleeding is much greater than that for chronic bleeding. Therefore, it is important to understand the pathogenesis of acute GI bleeding, with an emphasis on early detection, prevention, and intervention, in order to minimize morbidity and mortality.

Acute Gastrointestinal Bleeding: Diagnosis and Treatment covers a wide range of topics, with particular emphasis on the pathophysiology, diagnosis, management, and treatment of various acute bleeding disorders. The general approaches to the acute GI bleeding patient are discussed in terms of supportive care, early detection and determination of upper vs lower GI bleed, when to transfuse, as well as early predictors of morbidity and mortality. Outlined in this volume are the many dilemmas faced by physicians in the approach to the acute GI bleeding patient, such as localization of the bleeding source (upper vs lower), the need and timing for emergent endoscopy, and the timing for radiologic intervention and/or surgery. The emphasis throughout is on patient management, diagnostic measures, and treatment modalities. Diagnostic and treatment algorithms for acute GI bleeding determined by evidence-based medicine and standard-of-care issues are included.

We hope that this book serves as a useful reference for both primary care physicians as well as gastroenterologists.

Karen E. Kim, *MD*

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I Epidemiology

1 Epidemiology of Acute Gastrointestinal Bleeding

Phillip Chung, MD
and Karen E. Kim, MS, MD

Gastrointestinal (GI) bleeding is an extremely common clinical problem, resulting in significant morbidity, mortality, and cost. There are over 300,000 hospitalizations annually in the United States for GI bleeding *(1)*, accounting for 1–2% of all hospital admissions *(2)*. A conservative estimate of the overall annual cost of hospital admissions for GI bleeding is $900 million *(3)*, but the true overall cost, including outpatient endoscopic and radiologic investigations, clinic visits, and work days lost, far exceeds this figure.

The overall incidence of upper GI bleeding is approximately 100 cases per 100,000 population *(4,5)*. Acid peptic disease (e.g., gastric and duodenal ulcers as well as gastritis) is the most common cause of upper GI bleeding, accounting for 50–75% of all cases *(6–8)*, even among patients with chronic alcohol use, portal hypertension, and varices *(9)*. Furthermore, the predominance of peptic ulcer bleeding has not been affected by the advent of improved acid suppression with medical therapy *(6)*. Acid peptic disease is followed by variceal bleeding, gastric and duodenal erosive disease, and Mallory-Weiss tears in prevalence, each accounting for approximately 15% of the overall incidence *(8,10)*. The elderly appear to be at particular risk, as the proportion of elderly patients who present with upper GI bleeding has steadily increased, with persons older than age 60 years accounting for 35–45% of all cases *(11)*. This increase cannot be explained by demographics alone, as increasing age directly correlates with an increased rate of hospitalization for upper

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GI bleeding, even after correcting for the age distribution of the population *(4)*.

Lower GI bleeding is far less common, around 20–27 per 100,000 *(12)*. It should be noted that although 80% of patients with GI bleeding pass heme per rectum as bright red blood, maroon stools, or melena, only 24% of all GI bleeding is from a lower GI source *(13,14)*. The incidence of lower GI bleeding is higher in men than women, for unknown reasons, and, as with upper GI hemorrhage, the elderly are at increased risk. The rate of hospitalization for lower GI bleeding increases more than 200-fold from the third to the ninth decades, probably because of an increased incidence of the most common etiologies; diverticulosis, angiodysplasia, and neoplasia in the elderly *(12,15)*. In most studies, diverticulosis is the most common cause of acute lower GI bleeding, accounting for 42–55% of cases *(12,16)*. However, in one large series of patients with severe, persistent hematochezia, angiodysplasia was the most common diagnosis, accounting for 30% *(17)*. Other, less common etiologies include colorectal neoplasia, colonic ischemia, inflammatory bowel disease, infectious causes (particularly *Salmonella* and *E. coli* O157:H7), radiation proctitis, stercoral ulcers, iatragenic causes (e.g., postpolypectomy, endoscope trauma, prep trauma, and so on), intussusception, solitary rectal ulcer syndrome, colonic varices, and endometriosis *(16)*. Hemorrhoidal bleeding is probably the most prevalent cause of acute GI bleeding in the ambulatory setting, accounting for up to 76% of cases, but it represents only 2–9% of admissions for lower GI bleeding *(12,18,19)*.

The overall mortality rate for all gastrointestinal bleeding is approximately 5–12% *(20)*. Over the past 45 years, the mortality from upper GI bleeding has remained stable at approximately 10%, accounting for approximately 10–20,000 deaths annually, despite improved diagnostic and therapeutic modalities *(20)*. This may reflect, in part, the aging population, which has a significantly higher GI bleeding mortality *(11,16)*.

In contrast to upper GI hemorrhage, the mortality from lower GI bleeding has decreased dramatically over the past two decades, despite the similarly higher risk among the aging population. Most recent studies have found the mortality rate of acute lower GI bleeding to be below 5% and to be largely caused by vascular events rather than hemorrhage *per se (12,18,21,22)*. This is probably the result of earlier detection and improvements in therapeutic modalities.

In 5–10% of cases of GI hemorrhage, no source is identified within the reach of standard bidirectional endoscopy *(23,24)*. Among these patients, 27–40% will have lesions in the small bowel *(25,26)*. Despite

the development of diagnostic modalities, such as angiography, push enteroscopy, and sonde enteroscopy, approximately 50% of these lesions are not diagnosed prior to surgery *(27)*. Even the gold standard diagnostic modality, intraoperative enteroscopy, is diagnostic in only 55% *(28)*. Overall, the most common cause of small intestinal bleeding is vascular lesions, accounting for 70–80% *(29)*. The most common vascular lesions are angiodysplasias, or vascular ectasias, which represent 63% of identifiable bleeding lesions in the small bowel *(30)*. Whether the endoscopic identification of angiodysplasias is truly representative of their incidence as the source of small bowel hemorrhage is questionable. In the colon, the prevalence of this lesion as an incidental finding far exceeds the incidence of bleeding, as bleeding occurs in less than 10% of all patients with angiodysplasias found during colonoscopy *(24)*. Other common vascular lesions include arteriovenous malformations, venous ectasia, telangiectasias, hemangiomas, and Dieulafoy's lesions *(24)*. In patients younger than 50 years of age, small bowel tumors are the most common cause of small bowel bleeding, and they are the second most common etiology overall, accounting for 5–10% *(31,32)*. In older patients, angiodysplasias are the most common etiology, probably reflecting their increased incidence with aging *(27)*. Other causes of small bowel hemorrhage include ulcerations (particularly those induced by nonsteroidal antiinflammatory drugs), Crohn's disease, diverticula, varices, duplication cysts, infectious enteritis, intussusception, ischemia, vasculitis, and Meckel's diverticulum.

Acute gastrointestinal bleeding is an extremely common clinical condition affecting a large patient population. The diverse clinical presentations, etiologic factors and treatment modalities are important to understand, and early identification of the source of bleeding is, the essential component in reducing morbidity and mortality. The following chapters discuss acute upper and lower gastrointestinal bleeding, with an emphasis on diagnosis and treatment.

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II Upper Gastrointestinal Bleeding

2 Nonvariceal Esophageal Bleeding

Christian Stevoff, MD
and Ikuo Hirano, MD

CONTENTS

INTRODUCTION

The esophagus is an important site of acute upper gastrointestinal (GI) bleeding that typically presents with hematemesis or melena. A careful history is essential in assembling an accurate differential diagnosis. An antecedent history of vomiting, immunosuppression, medication use, and instrumentation in addition to symptoms of heartburn, dysphagia, and odynophagia is helpful in establishing a diagnosis.

The esophageal mucosa is normally devoid of large vessels that could cause rapid blood loss if damaged. In the absence of varices or bleeding diathesis, acute esophageal bleeding is caused by deep injury to the esophagus or abnormally superficial arterial branches. As it is common for many of the conditions discussed below to lead to shallow ulceration of the esophagus, it is more likely for esophageal bleeding to present

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Table 1
Causes of Nonvariceal Esophageal Bleeding

- Mallory-Weiss tear
- Peptic esophagitis
- Infectious esophagitis
  - Viral
    - Herpes simplex
    - Cytomegalovirus
    - HIV
      - Primary
      - Bacillary angiomatosis
      - Nocardia
      - Actinomycoses
      - Mycobacterial
    - Epstein-Barr virus
    - Varicella zoster
    - Human papillomavirus
  - Bacterial
    - Tuberculosis
    - Syphilis
    - *Mycobacterium avium-intracellulare*
    - Actinomycosis
    - Other—*Staphylococcus aureus*, *Staphylococcus epidermis*, *Staphylococcus viridans* (hard to prove as primary cause)
  - Fungal
    - *Candida albicans*
    - Blastomycosis
- Caustic injury/pill esophagitis
- Neoplastic causes
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Lymphoma
  - Stromal tumor
  - Metastatic disease—breast, melanoma, and other
  - Melanoma
  - Small cell carcinoma
  - Kaposi's sarcoma
  - Hemangioma
  - Squamous papilloma
  - Liposarcoma
- Cutaneous disorders
  - Epidermolysis bullosa
  - Pemphigus vulgaris

with a subacute or chronic course. However, given the high prevalence of conditions such as gastroesophageal reflux disease, the esophagus is a significant source of acute GI blood loss, accounting for approximately one-third of all acute upper GI bleeding cases.

Table 1 ***(continued)***

Cutaneous disorders
Bullous pemphigoid
Cicatracial pemphigoid
Tylosis
Erythema multiforme
Pseudoxanthem elasticum
Lichen planus
Stevens-Johnson syndrome
Inflammatory causes
Crohn's disease
Eosinophilic esophagitis
Sarcoidosis
Collagen vascular disease
Wegener's granulomatosis
Anti-cardiolipin antibody syndrome
Behçet's disease
Henoch-Schönlein purpura
Scleroderma
Amyloidosis
Ischemic esophagitis ("black esophagus")
Iatrogenic causes
Radiation
Chemotherapy
Graft-versus-host disease
Surgery
Photodynamic therapy
Endoscopy/transesophageal echocardiography for diagnosis or dilation
Sclerotherapy/banding
Vascular causes
Dieulafoy's lesion
Blue rubber bleb nevus syndrome
Arteriovascular malformation
Esophagoaortic fistula
Subclavian artery-esophageal fistula
Miscellaneous causes
Gastric inlet patch
Fibrovascular polyp
Esophageal intramural hematoma
Scurvy
Esophageal diverticulum
Foreign body

There are numerous causes of esophageal bleeding (Table 1). This chapter discusses specific etiologies with particular emphasis on the more common and clinically pertinent etiologies. Esophageal varices are the subject of another chapter in this book.

MALLORY-WEISS LESIONS

Mallory-Weiss lesions are tears occurring at or near the esophagogastric junction, secondary to mechanical stress most commonly induced by vomiting. Increased intraabdominal pressures during retching or vomiting combined with forceful propulsion of the gastric cardia through the diaphragmatic hiatus may cause enough force to lacerate the esophagogastric mucosa.

Mallory-Weiss lesions account for 4–14% of all cases of acute upper GI bleeding in patients who undergo endoscopy *(1,2)*. Most series report a male predominance of 60–80% *(3–6)*, with the mean age typically in the fourth to sixth decades *(3,6,7)*. Recent alcohol ingestion has been reported in 21–80% of cases *(5,8,9)*. Importantly, a history of antecedent vomiting or retching is only reported in 30–85% of patients *(1,2,6)*. Hematemesis is a presenting symptom in 85–95% of cases *(2,9)*. Any condition causing vomiting could produce a tear, including coughing, cardiopulmonary resuscitation, pregnancy, and even colonoscopy preparation *(10–14)*. A Mallory-Weiss tear secondary to endoscopy is uncommon and rarely leads to severe bleeding *(13,15)*.

The diagnosis of Mallory-Weiss lesions is best made endoscopically with close inspection of the gastroesophageal junction. Barium swallows have poor sensitivity and are not recommended. The lesion is longitudinal, most commonly along the posterior aspect of the lesser curve of the gastric cardia, extending proximally to include the distal esophagus (Fig. 1) *(6)*. In over 80% of cases, a single tear exists *(5,6)*, averaging 0.5–5 cm in length *(16)*. Although esophageal involvement is common, only rarely is the lesion confined to the esophagus alone *(6,17,18)*. The presence of hiatal hernia is associated with a more distal laceration, perhaps sparing the esophagus altogether *(18)*. This is probably caused by proximal displacement of the esophagogastric junction from the diaphragmatic hiatus. Such lesions need to be distinguished from Cameron's erosions, although the latter typically presents with chronic GI blood loss. Several series have reported up to a 75% prevalence of hiatal hernias in patients presenting with bleeding Mallory-Weiss lesions *(5,16,18)*; however, one large series reported only 17% *(6)*.

The bleeding associated with Mallory-Weiss lesions is usually self-limited, with spontaneous cessation of bleeding reported in 90% of cases *(6)*. Protracted bleeding can occur, however, and active bleeding has been noted endoscopically in 25–55% of patients *(6,9)*. In 20–50% of cases, hypotension < 100 mmHg and tachycardia > 100 bpm are presenting features *(9,16)*, and 30–75% require blood transfusion dur-

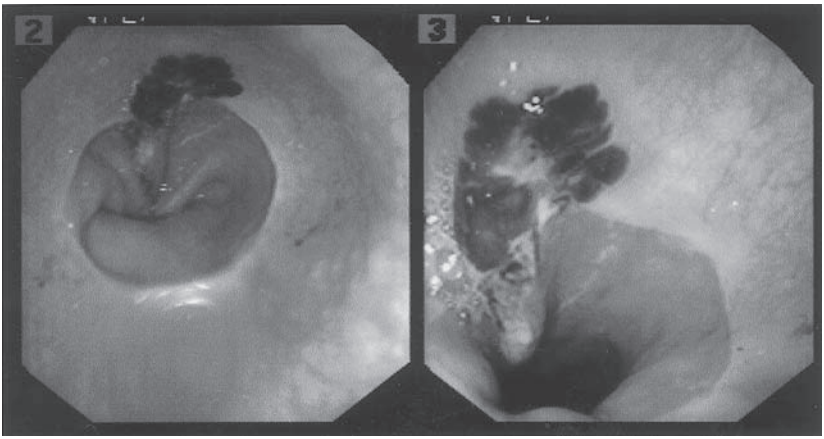

Fig. 1. Endoscopic view of a Mallory-Weiss tear straddling the squamocolumnar junction in the presence of a hiatal hernia

ing the hospital course *(5,6)*. A mortality of 0–13% has been reported in patients presenting with Mallory-Weiss lesions; however, not all the deaths were attributed to bleeding *(3,19–21)*. A recent series *(1)* attempted to define characteristics that would select a subset of patients with bleeding Mallory-Weiss lesions who exhibited a low likelihood of rebleeding, thereby not requiring admission to the hospital. The study noted that patients with portal hypertension or bleeding diathesis, including that caused by nonsteroidal antiinflammatory drugs (NSAID) use, were at increased risk of rebleeding. Patients with active bleeding at endoscopy were more likely to be treated endoscopically and received more blood transfusions.

Several endoscopic therapies have been described in the treatment of actively bleeding Mallory-Weiss lesions; however, few data exist to measure these modalities against each other or against no treatment at all. Endoscopic therapy for bleeding Mallory-Weiss lesions has included endoscopic electrocoagulation *(22)*, epinephrine injection *(23)*, or heater probe cauterization *(24)*. More recently, endoscopic band ligation similar to that used for bleeding esophageal varices has been utilized *(25,26)*. To date, however, no randomized, controlled trials have been performed to evaluate the efficacy of these modalities. Other modalities described in cases of failed endoscopic therapy include angiographic localization and embolization of the bleeding vessel *(27)*, which is a reasonable second-line approach. Placement of Sengstaken-Blakemore tube, although reported *(28)*, is no longer recommended for this condition

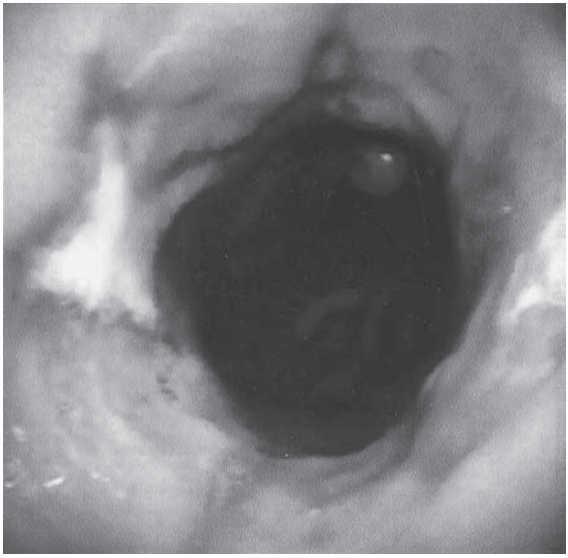

Fig. 2. Severe, erosive reflux esophagitis.

because of the substantial morbidity of the procedure itself. Surgery may be necessary to oversew the bleeding lesion if hemostasis cannot be achieved *(5,6,19,21)*. Although the efficacy of acid suppression in the treatment of Mallory-Weiss tears has not been studied, many patients are empirically placed on an antisecretory medicine *(21)*.

REFLUX ESOPHAGITIS

Gastroesophageal reflux disease (GERD) is a very common disorder, causing monthly symptoms in up to 36% of the U.S. population *(29)*. GERD occurs as a result of an abnormally prolonged exposure of the esophageal mucosa to gastric acid and pepsin. Reflux esophagitis occurs in a subset of patients with GERD in whom esophageal inflammation is visible as erosions or ulcerations (Fig. 2); it is found in 2–4% of the U.S. population *(30)*.

Reflux esophagitis is a common lesion of the upper GI tract found in the evaluation of GI bleeding. In a study of 248 patients with a mean age of 61 years who presented with positive fecal occult blood tests, esophagitis was detected in 9.3% and was the most common endoscopic abnormality *(31)*. In a separate study with a similar population, the same investigators found esophagitis to be one of the most common endoscopic abnormalities in patients presenting with iron deficiency anemia

(32). In several series, reflux esophagitis accounted for only 2–5% of all cases of acute upper GI bleeding, occurring less commonly than peptic ulcer disease (57–75%), esophageal varices (7–9%), or Mallory-Weiss tears *(19,20,33,34)*. However, in one recent study, reflux esophagitis accounted for 14.6% of overt upper GI tract bleeding *(35)*. The bleeding associated with acid reflux is not typically massive. In two large series, there were no deaths attributed to bleeding from reflux esophagitis *(19,20)*.

Although reflux esophagitis presenting as acute GI bleeding is uncommon in the general population, there are subgroups for which it poses an increased risk. In a study of 248 patients presenting with acute upper GI bleeding (115 aged > 80 and 133 aged 60–69 years), 21.1% of cases in patients older than 80 years were attributed to reflux esophagitis, compared with 3.3% of patients 60–69 years of age ($p < 0.001$) *(36)*. In another study, 25 critically ill patients underwent endoscopy at the time of endobronchial intubation and were re-endoscoped 5 days later *(37)*. They all had nasogastric tubes in place and were receiving intravenous H-2 receptor antagonists. After 5 days of mechanical ventilation, 48% had reflux esophagitis. Severity of esophagitis was related to the gastric residual volume. Critical illness, mechanical irritation from the nasogastric tube, disruption of the normal lower esophageal sphincter barrier by the presence of a nasogastric tube feeding in the supine position, and decreased gastric emptying are proposed mechanisms for the development of esophagitis in this population *(36,38)*. A case-control, retrospective review of institutionalized mentally retarded adults admitted for acute upper GI bleeding revealed reflux esophagitis to be the most common diagnosis, accounting for 70% of cases *(39)*.

Bleeding associated with reflux esophagitis is almost always self-limited, requiring no further interventions acutely beyond hemodynamic support, elimination of aggravating factors (i.e., NG tubes), and acid suppression to initiate healing. Proton pump inhibitors are superior to all other therapy in the healing of reflux esophagitis *(40)*. If the esophagitis is severe, the patient should begin high-dose proton pump inhibition, and repeat endoscopy in 8–12 weeks should be considered to assess healing and evaluate for the presence of Barrett's esophagus.

ESOPHAGEAL INFECTIONS

Infections of the esophagus rarely manifest in the general population, being more common among immunocompromised hosts. Viral, fungal, and bacterial infections of the esophagus typically present

with dysphagia and/or odynophagia rather than acute upper GI bleeding. Most of the published literature regarding acute upper GI bleeding secondary to esophageal infection is in the form of case reports or small series.

Viral Esophagitis

Herpes Simplex Virus

Herpes simplex virus (HSV) types 1 and 2 have each been reported to cause esophagitis *(41,42)*. The most common presentation is that of acute-onset odynophagia and dysphagia, retrosternal pain, and fever. Other presenting symptoms may include nausea, vomiting, or hematemesis. Lesions progress from fragile 1–3-mm vesicles predominantly in the mid-to-distal esophagus that slough, to sharply demarcated, "punched-out" ulcers with raised margins. These lesions may coalesce and form a larger area of ulceration. Heaped up inflammatory exudates may collect in the base of the ulcers in severe cases, resembling *Candida* esophagitis *(43)*. One case report described a black esophagus, suggesting necrosis and eschar formation *(44)*. Biopsies and brushings should be taken from the margin rather than the ulcer base to improve diagnostic yield since herpes infects the squamous epithelium. Biopsies should be taken for both histologic examination and culture, as this increases the diagnostic yield *(45,46)*. Although immunostaining is also available, its diagnostic yield may not exceed that of histology and culture combined *(46)*. Oral or parenteral acyclovir is the first-line agent used in treatment of HSV esophagitis.

In a review of 23 cases of HSV esophagitis, 30% were associated with acute upper GI bleeding *(45)*. There are no reports of specific endoscopic or radiographic treatments for bleeding HSV esophagitis. However, there is one report of a patient with massive bleeding that resolved after treatment with intravenous acyclovir *(47)*.

Presentation of herpes esophagitis in the immunocompetent host is similar to that of the immunocompromised patient, but it is less common and the course is typically less severe. In a retrospective review of 38 cases of HSV esophagitis in otherwise healthy hosts, 76% presented with odynophagia, 50% with heartburn, and 45% with fever *(46)*. Only 21% displayed concurrent oropharyngeal lesions. The endoscopic appearance was similar to that of immunocompromised hosts, including friability (84%), numerous ulcers (87%), distal esophageal distribution (64%), and whitish exudates (40%). Only 68% of histologic examinations detected characteristic findings, further demonstrating the need for concurrent viral cultures, which were positive in 96% of those tested. Immune serologies were consistent with primary infection in 21% of

cases. Although most cases were mild and self-limited, there was a report of acute hemorrhage and esophageal perforation.

Cytomegalovirus

Cytomegalovirus (CMV) esophagitis typically has a more subacute presentation than HSV esophagitis *(48)*. Initial symptoms such as weight loss, nausea, vomiting, fever, and diarrhea often reflect the more systemic nature of the infection. Odynophagia, dysphagia, or hematemesis may subsequently develop, alerting the clinician to the possibility of esophageal involvement. As with HSV, the distribution of lesions in CMV esophagitis is commonly in the mid-to-distal esophagus *(49)*. The ulceration is usually shallow, with flat margins, and may extend for several centimeters. However, in some cases deep ulcers may occur *(49)*. In contrast to HSV esophagitis, biopsies should be taken from the center of the ulcer for optimal results *(48)*. CMV produces intranuclear inclusion in macrophages that are not commonly detected in squamous epithelium. As with HSV, cultures in addition to histopathology increase the diagnostic yield of biopsies *(50)*. Gancyclovir is the first-line agent in the treatment of CMV esophagitis. Although rare, infections in immunocompetent individuals do occur *(51,52)*.

In a review of 33 patients with CMV esophagitis, 5 presented with acute upper GI bleeding *(49)*. In this study, 8% of all patients showed deep ulceration. There are also reported cases of CMV esophagitis causing massive GI hemorrhage necessitating emergent esophagectomy after failure of medical therapy *(53)*. There are no reports of either acute endoscopic or angiographic treatment of this condition.

Other Viral Infections

Other rare viral causes of bleeding esophageal lesions include varicella zoster virus, human papillomavirus, and human immunodeficiency virus (HIV) (Fig. 3) *(54,55)*. There are reports of isolation of HIV from esophageal ulcers in infected patients *(56)*, suggesting a pathologic role of the virus. However, the role of HIV in the development of esophageal ulceration is still unclear, as the presence of HIV in the esophageal mucosa is common and often is independent of esophageal pathology *(55,57)*.

Fungal Esophagitis

Candida Esophagitis

Candida albicans is a yeast that is found as part of the normal human oropharyngeal flora. It is a common cause of esophagitis in immunocompromised patients, including those with AIDS, or diabetes mellitus, those on immunosuppressive medications, and the elderly. Many

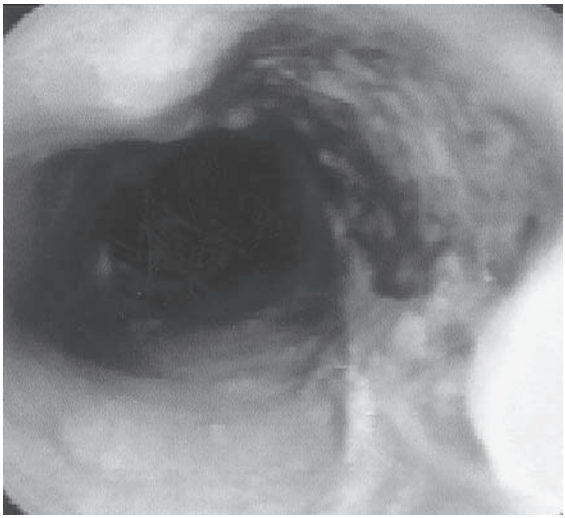

Fig. 3. Large, deep midesophageal ulceration in patient with AIDS. Viral cultures and histology did not reveal a pathogen or neoplasm consistent with an idiopathic HIV-related esophageal ulceration.

patients are asymptomatic, and infection is often found incidentally during investigation of another problem. Patients who are more immunosuppressed are typically more likely to be symptomatic, reflecting a more aggressive course of infection. The most common presenting symptoms are odynophagia or dysphagia. The endoscopic appearance of *C. albicans* esophagitis ranges from a few raised white plaques to confluent, elevated plaques with ulceration and buildup of "cottage cheese" material that may narrow the lumen *(58)*. Biopsies and brushings should be obtained for diagnosis; however, treatment is often empiric, based on endoscopic findings alone. Although oral thrush is a common finding, its absence should not rule out the diagnosis *(59,60)*.

Although rare, acute upper GI bleeding secondary to *C. albicans* esophagitis has been reported *(61)*. In one report, massive hemorrhage developed in a man with a history of renal failure *(62)*. In this patient, supportive care was continued until intravenous therapy with amphotericin B could initiate healing. In another, acute bleeding was noted in an alcoholic patient with esophageal ulcerations secondary to *C. albicans* in the setting of two epiphrenic diverticula *(63)*.

Other Fungal Infections

Blastomycosis dermatitidis is a rare cause of esophagitis and has been reported to cause acute upper GI bleeding *(64)*. *Histoplasma* spe-

cies are common pulmonary mycoses that may affect the esophagus by direct extension from the lung and mediastinum, or via hematogenous spread *(65)*. *Aspergillus* species are mycoses commonly affecting patients with underlying pulmonary disease. Although esophageal infection has been documented *(69)*, there are no reports of acute bleeding secondary to this pathogen. Treatment is supportive and includes antifungal therapy.

Bacterial Infections

Mycobacterium tuberculosis

Although *Mycobacterium tuberculosis* may infect any organ in the body, clinically significant esophageal involvement is rare. In immunocompromised cases, disseminated disease is common and can present with esophageal manifestations and symptoms that include dysphagia and chest pain. Esophageal infection may occur by hematogenous spread or direct extension from mediastinal lymph nodes. Endoscopically, the lesions appear as shallow ulcerations that range in size. Fistulae may be noted, as well as traction diverticula in the midesophagus secondary to scarring and retraction of mediastinal nodes *(70)*. Extrinsic compression may be seen as well *(71)*. Biopsies should be taken for routine histology, acid-fast smears, and mycobacterial culture.

There are several reports of acute upper GI bleeding from this condition, often secondary to fistulizing complications *(72–74)*. In a review of 11 patients with tuberculous esophagitis at a single institution over an 18-year period, two presented with hemorrhage *(70)*. When hemorrhage results from mucosal ulceration without fistula and is self-limited, medical management alone is reasonable.

Other Bacterial Infections

Rupture of a syphilitic aortic aneurysm into the esophagus of a patient resulting in massive hemorrhage and death has been reported *(75)*. Invasive bacterial esophagitis caused by normal oropharyngeal flora has been reported to occur in immunosuppressed patients, particularly in those with granulocytopenia *(76)*. Mucosal friability, pseudomembranes, and ulceration can be present *(76,77)* and may lead to bleeding, especially in the setting of a bleeding diathesis. Treatment with broad-spectrum antibiotics is generally sufficient.

MALIGNANT NEOPLASM

Malignant tumors of the esophagus, either primary or metastatic, are another cause of acute upper GI bleeding. Neovascularization as well as deep invasion of larger tumors can lead to such a complication. The most

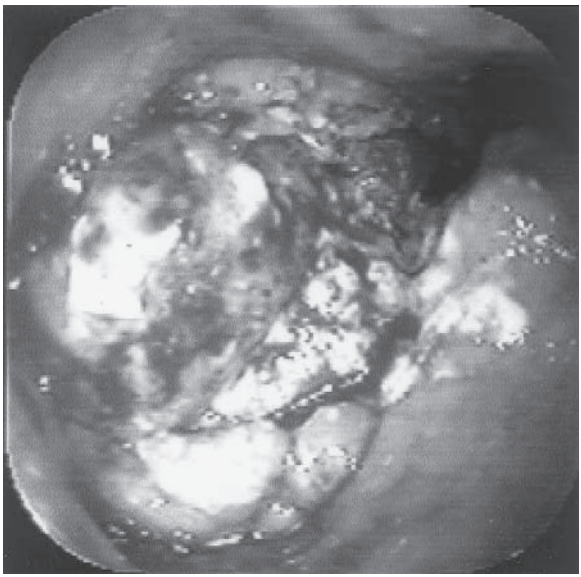

Fig. 4. Distal esophageal exophytic mass with biopsies revealing adenocarcinoma.

common primary malignancies of the esophagus are squamous cell carcinoma and adenocarcinoma, which account for more than 90% of all such lesions. Reports of rare primaries include malignant melanoma presenting as acute hemorrhage *(78)*, and esophageal stromal tumor typically presenting with dysphagia but rarely with acute bleeding *(79)*. Reported cases of bleeding from metastases include breast carcinoma *(80)*, renal cell carcinoma *(81)*, small cell carcinoma, osteogenic sarcoma, and germ cell tumors *(82)* (Table 1).

Endoscopically, esophageal carcinoma appears as a mucosal mass lesion that is often exophytic and ulcerated (Fig. 4). There are clinical characteristics of squamous cell carcinoma and adenocarcinoma, however, that may help influence clinical suspicion prior to the interpretation of biopsies. The most common site of squamous cell carcinoma is the midesophagus, whereas adenocarcinoma is frequently located in the distal esophagus. Although both cancers increase in incidence with age and male gender, specific risk factors for squamous cell carcinoma include African-American race and tobacco and alcohol use. Adenocarcinoma is more prevalent among Caucasians, with the primary risk factors being Barrett's esophagus and GERD. Although both are relatively uncommon cancers, the incidence of esophageal adenocarcinoma is rapidly increasing.

Esophageal carcinoma presenting as spontaneous acute upper GI bleeding is rare, with the dominant presenting symptom being dysphagia and weight loss. Large series have reported only rare cases of acute bleeding as the initial symptom *(19,20,34)*. There is a reported case of a distal esophageal carcinoma that penetrated the aorta, leading to fistula, massive hematemesis, and death *(83)*. In another case, a primary esophageal malignant melanoma presented with massive hematemesis *(78)*.

Acute bleeding in patients with esophageal carcinoma has been more commonly reported after treatment with radiation or metal stenting of the lesion. In a series of 423 consecutive patients with esophageal cancer treated with radiation therapy, 31 (7%) developed massive hemorrhage and died *(84)*. The mean interval from start of radiation until hemorrhage was 9.2 months. Risk factors included total dose exceeding 70 Gy, active infection, and metal stent placement. Eight of 22 patients (36%) receiving more than 80 Gy developed fatal massive hemorrhage. Prior chemotherapy and radiation were associated with acute upper GI bleeding that developed in 7/22 patients (32%) compared with 1/37 (3%) patients without prior treatment. An early report describes four patients who had recently completed radiation therapy for esophageal carcinoma that was complicated by fatal hemorrhage; two of the patients developed aortoesophageal fistulae *(85)*. In contrast, another retrospective study of 60 cases reported no increased risk of life-threatening complications after chemotherapy or radiation *(86)*. Although it is intuitive that radiation or chemotherapy increases tissue destruction, potentially increasing the likelihood of hemorrhage, the natural history of esophageal tumors in the absence of metal stenting or radiation is poorly defined. Stenting an obstructing cancer might allow the tumor to progress to the point where it would have bled even in the absence of stenting.

No large series have examined the efficacy of therapeutic modalities in the treatment of acutely bleeding esophageal carcinoma. Cases of ethanol injection *(87)* and selective arteriography with embolization *(88)* have been reported. In a small series examining the use of argon-plasma coagulation, bleeding was controlled successfully in three of five cases *(89)*. The use of endoscopic laser devices has been reported for palliation of obstructing cancers *(90,91)*, although its effectiveness for bleeding has not been reported. Novel technologies such as endoscopic cryotherapy *(92)* are currently being studied.

MISCELLANEOUS CONDITIONS

Esophageal Dieulafoy's Lesion

Dieulafoy's lesion is an abnormal submucosal artery in the GI tract characterized by recurrent episodes of acute gastrointestinal hemor-

rhage. The most common location is the proximal stomach, where the lesion appears as a reddish protuberance within normal mucosa. Its appearance is subtle; without active bleeding on endoscopy, it may be missed altogether. Extragastric Dieulafoy's lesions are rare but have been reported, in the esophagus *(93,94)*. Epinephrine injection *(95)* and endoscopic band ligation *(96)* have been reported as successful treatment options in the management of esophageal Dieulafoy's lesions.

Iatrogenic Causes

Several iatrogenic causes have been reported as causes of esophageal bleeding (Table 1). Bleeding may complicate routine endoscopic procedures, but more commonly it is a complication of therapeutic endoscopy. Such procedures include esophageal variceal sclerotherapy or banding, esophageal biopsies, photodynamic therapy, and dilation. Bleeding is a well-recognized albeit rare complication of all forms of esophageal dilation including mercury bougienage (Maloney dilators), polyvinyl dilators (Savary-Guillard), and balloon dilators. Most studies report a risk of bleeding of less than 0.5% with esophageal dilation.

The relationship of nasogastric intubation and GERD in the development of esophagitis has already been discussed. However, independent of acid reflux, the presence of a nasogastric tube itself may lead to significant esophageal erosions over time *(37,97)*. These lesions, secondary to mechanical trauma, are more likely to be located in the proximal esophagus and appear to be linear in nature. If possible, the nasogastric tube should be removed. There are reports of vascular esophageal fistula development causing massive hemorrhage secondary to nasogastric tube use, but this complication is very rare *(98)*.

Systemic chemotherapy may lead to mucositis involving the entire GI tract, including the esophagus. Mucositis is a common side effect of standard chemotherapeutic regimens, as well as those used in bone marrow transplantation. Agents that predispose to this condition include dactinomycin, bleomycin, cytarabine, daunorubicin, vincristine, 5-fluorouracil, and methotraxate. Esophageal injury usually begins to occur shortly after blood counts reach their nadir. The esophageal mucosa becomes friable and may slough or ulcerate. Bleeding can occur, particularly in patients who are thrombocytopenic. The mucositis may be severe but is usually self-limited. It is important to differentiate between this and infectious etiologies, as patients receiving chemotherapy are immunocompromised and are therefore at risk for opportunistic infection. It is rare to have esophageal involvement secondary to chemotherapy without oropharyngeal involvement, and odynophagia is likely to be present. When significant bleeding occurs, support with

blood products including platelets should be continued until the condition resolves. This may take several days and usually commences when blood counts begin to recover.

Radiation therapy to the chest may lead to acute esophageal injury. Acute radiation esophagitis typically occurs 2–3 weeks after initiating therapy, with erosions and ulcerations that may persist for several weeks after its conclusion. Chest pain and dysphagia are common associated symptoms. The severity of esophagitis is related to the dose of radiation. At doses greater than 40 Gy, edema and redness become more frequent; moderate to severe esophagitis becomes more likely as the dose nears 60–70 Gy *(99,100)*. Concomitant chemotherapy potentiates radiation damage, and significant esophagitis may be seen with as little as 25 Gy *(101)*. Although some studies report success in improving symptoms and severity of radiation esophagitis with sucralfate *(102)*, others have not reproduced these results *(103)*.

Graft-versus-host disease (GvHD), most commonly seen after bone marrow transplantation, may involve the esophagus and may present with dysphagia, odynophagia, or chest pain. Chronic GvHD seen weeks to months after transplantation involves the esophagus more extensively than does acute GvHD *(104)*. Endoscopy may reveal generalized friability and desquamation in the esophagus. Severe cases may lead to esophageal bleeding or stricture formation dilation *(105)*. Treatment includes immunosuppressive medications such as glucocorticoids or azathioprine.

Drug toxicity may take several forms in the GI tract, including Stevens-Johnsons syndrome, a desquamating condition that may occur secondary to therapy with many drugs, most commonly antibiotics such as penicillins or sulfa-based products. Diffuse GI ulceration and sloughing may occur, leading to melena, hematochezia, or hematemesis. Extensive necrosis with lymphocytic infiltration and apoptosis occurs; lesions are histologically similar to those seen in chronic GvHD. Supportive care and withdrawal of offending agents is the mainstay of management. Use of immunosuppressive agents is controversial for early disease, and these are generally not helpful for advanced disease *(106)*.

Pill Esophagitis and Caustic Ingestion

Pill esophagitis has been reported after the use of multiple medications including NSAIDS, tetracycline, erythromycin, potassium chloride, and bisphosphonates. Typically presenting with acute onset of odynophagia, the lesions are ulcers caused by direct toxicity to esophageal mucosa by pills that may fail to clear the esophagus normally during swallowing. The ulcers may be deep and extensive, and they

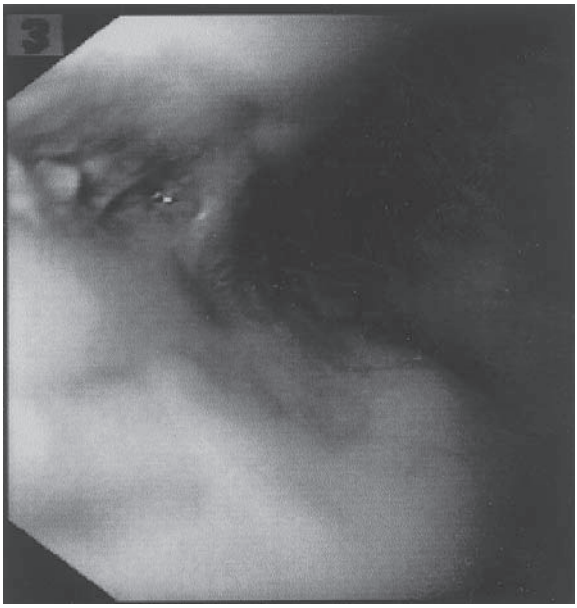

Fig. 5. Midesophageal ulceration in a patient presenting with odynophagia and a history of ingestion of tetracycline.

usually occur in the midesophagus (Fig. 5). Although cases are most often self-limited, complications that include hemorrhage, stricture, and perforation can occur *(107)*. Care should be taken to evaluate for signs of perforation by monitoring vital signs, examination for crepitus in the chest and neck, and chest radiograph if doubt persists. Patients should be encouraged to sit upright and take an adequate amount of fluid with pills to minimize the risk of this condition. Topical agents such as sucralfate or lidocaine are sometimes used for symptomatic relief, although there are no data on their efficacy. Endoscopic evaluation is recommended when the diagnosis of pill esophagitis is uncertain or in cases of significant hemorrhage.

Ingestion of strongly acid or alkaline solutions may lead to rapid and severe esophageal injury. Alkali injury leads to liquefaction necrosis and deeper injury than the coagulation necrosis associated with acid ingestion. The mucosa may become friable or deeply ulcerated and may perforate in severe cases. Esophageal injury may be present in the absence of oral lesions *(108)*. Dysphagia, odynophagia, hematemesis, hoarseness, or stridor may develop. Optimal timing of endoscopy is controversial; endoscopy is contraindicated if suspicion of perforation exists. If the esophagus appears erythematous or displays nonconfluent

ulceration, supportive care and observation are adequate. The presence of circumferential lesions or deep ulcers with eschar formation is more predictive of subsequent stricture formation, and follow-up endoscopy should be performed regularly to assess for stricturing. Over time, repeated dilation may be necessary. Glucocorticoids, once thought to be beneficial in prevention of strictures, are no longer used. In the absence of suspicion of perforation, antibiotics are generally not indicated. Neutralization of the substance should never be performed because the resultant heat production may add further thermal injury to the already injured tissue. Carcinoma of the esophagus is a late complication of lye ingestion, with a 1000–3000-fold increase in the incidence of squamous cell carcinoma of the esophagus; the average interval is 40 years after ingestion *(109)*.

Systemic Inflammatory Disorders

Crohn's disease rarely involves the esophagus *(110)*. Associated lesions include aphthous lesions, inflammatory strictures, fistulae, polyps, and large ulcers. Although these lesions may bleed acutely, there are no reported cases of acute upper GI bleeding attributed to Crohn's disease isolated to the esophagus, perhaps because of the exceedingly rare nature of this complication. Treatment with topical agents is often ineffective owing to the proximal distribution of the disease. Systemic immunomodulatory agents may be necessary to control Crohn's disease of the esophagus.

Several systemic cutaneous disorders may lead to diffuse esophageal involvement. Epidermolysis bullosa comprises several rare disorders in which blister formation occurs after minor trauma. Dysphagia, pain, and bleeding may result *(111)*. Pemphigus vulgaris is an autoimmune disorder in which large bullae form spontaneously, commonly affecting the esophagus. Esophageal bleeding is less common yet possible in bullous pemphigoid, a chronic disease characterized by bulla formation and circulating autoantibodies to the basement membrane. Corticosteroids are used in the management of all these disorders. Stricturing is possible, and dilation may be necessary *(111,112)*.

Esophagitis secondary to collagen vascular diseases has been reported, including Wegener's granulomatosis and anticardiolipin antibody syndrome *(113,114)*. Reflux esophagitis may complicate scleroderma owing to poor peristaltic activity of the esophageal smooth muscle and hypotension of the lower esophageal sphincter. Treatment is based on the specific disorder.

Hemangioma

Hemangioma of the esophagus has been reported as a rare cause of acute esophageal bleeding *(115)*. There is also a report of recurrent

massive acute upper GI bleeding attributed to a vagal neurilemoma diagnosed at thoracotomy *(116)*. When possible, endoscopic therapy should be attempted. If bleeding persists, surgical intervention may be necessary.

Esophagoarterial Fistula

Esophagoaortic fistulae formations in the setting of esophageal carcinoma or nasogastric intubation have already been discussed. There has been a single report of esophagoaortic fistula presenting with massive bleeding attributed to reflux esophagitis *(117)*. There is also a report of periesophageal abscess leading to esophagoaortic fistula formation and massive bleeding *(118)*. Esophageal foreign body ingestion may lead to fistula formation in vascular structures of the chest. Impaction of a fishbone in the esophagus has led to fistula formation in the subclavian artery *(119)*. There are several reports of foreign body ingestion by children and adults that have caused esophagoaortic fistula formation *(120,121)*. Management is surgical, as bleeding is often life-threatening and not amenable to endoscopic management.

CONCLUSIONS

Nonvariceal esophageal bleeding is a common cause of acute upper GI hemorrhage. The differential diagnosis of nonvariceal esophageal bleeding is large, and the condition often requires endoscopy for accurate diagnosis. In general, the more common causes of acute esophageal hemorrhage are self-limited or respond to conservative management. Massive, acute bleeding, however, does occur. Prompt diagnosis is important, as the treatments of the various disorders are quite diverse and include medical, endoscopic, and surgical management.

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3 *Helicobacter pylori* and Peptic Ulcer Disease

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CONTENTS

INTRODUCTION

Peptic ulcer disease is a common gastrointestinal (GI) problem that has a substantial impact on patient well-being and health care costs. Complications include hemorrhage, perforation, and gastric outlet obstruction. Etiologies underlying peptic ulcer disease include *Helicobacter pylori* (*H. pylori*) infection, use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), rare disorders such as gastrinoma (Zollinger-Ellison syndrome), and opportunistic infections, particularly in immunosuppressed patients.

H. pylori has been linked to peptic ulcer disease as well as to gastritis, gastric adenocarcinoma, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and potential extragastric manifestations. The prevalence of infection varies worldwide, is inversely related to socioeconomic

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status, and consequently is higher in less developed societies. More recently, there has been a sharp decline in the prevalence in *H. pylori* infection worldwide, particularly in the Western world as well as the Far East. Nonetheless, *H. pylori* is still the cause of most peptic ulcer disease, and its diagnosis and eradication in patients with ulcers and complications such as bleeding will improve outcome.

EPIDEMIOLOGY

At the end of the 1980s, it was estimated that approximately 500,000 new cases of peptic ulcers occurred annually in the United States, and the lifetime risk of peptic ulcer disease was estimated at 5–10% *(1)*. More recent estimates of prevalence have been similar, at least 10% of Americans having a history of peptic ulcer disease *(2)*, with acute exacerbations annually leading to 8 million physician visits and 275,000 hospitalizations for a total of 3 million hospital days *(3)*. Traditionally peptic ulcer disease has been a disease of younger men, but now it appears to affect women and the elderly more frequently. Although overall hospitalization rates for peptic ulcer disease have decreased over the last several decades, hospitalizations (especially of elderly patients with ulcer-related complications such as bleeding and perforation) have increased *(4–6)*.

CLINICAL PRESENTATION

Abdominal pain is the principle symptom of peptic ulcer and is most commonly felt in the epigastrium. The quality of the discomfort, its pattern, and its associated symptoms such as vomiting may vary from patient to patient. In fact, the sensitivity and specificity of "characteristic" epigastric discomfort in predicting the presence of a peptic ulcer is actually quite low. Other possibilities in the differential diagnosis of "ulcer pain" include gastroesophageal reflux disease, angina, nonulcer dyspepsia, small and large intestinal conditions, gallstones, and pancreatic disorders. Furthermore, patients (especially those taking NSAIDs) frequently present with complications such as GI bleeding after a "silent" course and no pain. Nonetheless, there are classic symptomatic presentations in some patients that are worthy of mention. For example, the classic description of duodenal ulcer pain is a burning or gnawing sensation in the epigastrium, which characteristically occurs 1½–3 hours after eating, may awaken the patient at night, and is relieved within minutes by food or antacids ("pain-food-relief"). With a gastric ulcer, on the other hand, the pain may be triggered and not relieved by

food. Vomiting is unusual with uncomplicated peptic ulcer disease, but when it occurs, it often leads to pain relief.

DIAGNOSIS

Since history may not accurately predict ulcer disease, diagnostic testing is often necessary. Upper GI endoscopy [esophagoduodenoscopy (EGD)] is the most accurate test for diagnosing ulcers of the stomach and duodenum. A study comparing double-contrast barium upper GI X-rays with endoscopy found the diagnostic accuracy of upper GI series to be 65% and that of endoscopy 88% *(7)*. Unlike X-ray studies, endoscopy also allows biopsy of gastric ulcers to exclude cancer and for the detection of *H. pylori*. The location of a duodenal ulcer could be important in suggesting a possible cause. Most ulcers of the duodenum occur in the duodenal bulb. Postbulbar ulcers can occur in those infected with *H. pylori* or those using NSAIDs, but their presence should raise the possibility of other conditions such as gastrinoma or unusual infections in the appropriate patient.

Although these diagnostic studies are helpful in identifying ulcers, the appropriate type of patient with "ulcer-like" dyspepsia in which they should be done remains controversial. Only a small minority of those with dyspepsia (<20%) have gastric or duodenal ulcers, and malignancy is even less common *(8)*. In most patients with dyspepsia, no explanation is found for their symptoms during evaluation, and they are classified as having functional or nonulcer dyspepsia. Some have *H. pylori* infection, but the relevance of this organism in nonulcer dyspepsia is debatable since cure of infection will not predict symptom resolution.

Dyspepsia guidelines and algorithms abound intended to assist primary care providers and gastroenterologists to manage patients in an appropriate yet cost-effective manner. Based on its review of outcomes, cost, and age-related diagnoses, over 15 years ago the American College of Physicians recommended empiric acid antisecretory therapy without diagnostic testing as the initial approach in dyspeptic patients younger than 45 years of age without alarm signs or symptoms of organic disease (e.g., weight loss, anemia, bleeding, dysphagia, and so on). Initial endoscopy was reserved for those older than 45 years, for anyone with alarm features, and for those not responding to empiric treatment after 7–10 days *(9)*. The American Gastroenterological Association (AGA), utilizing comparable analyses, provided similar guidelines in 1998 but also addressed the role of *H. pylori (8)*. Early referral for endoscopy remains appropriate for older patients (>45 years old) with new-onset dyspepsia because the incidence of gastric cancer increases with

increasing age, and early endoscopy in such patients could increase the detection of early-stage gastric cancers, which may be more amenable to treatment *(8,10)*. In addition, initial endoscopy remains appropriate for patients with alarm symptoms regardless of age. For younger otherwise healthy patients, the AGA recommends initial empiric therapy with antisecretory medication or testing for *H. pylori* and treating infection when present (test and treat). If symptoms persist, then endoscopy should be done *(8)*.

Empiric treatment of *H. pylori* without first documenting an ulcer remains controversial since most dyspeptic individuals have nonulcer dyspepsia, for which treatment of *H. pylori* is only occasionally helpful *(11)*. Also, selecting age 45 rather than an older age as the cutoff to recommend EGD is debatable. For example, in a recent study from Scotland, 90% of patients younger than 55 years subsequently diagnosed with gastric cancer had at least one "sinister" symptom (dysphagia, weight loss, persistent vomiting, anemia, family history of upper GI cancer, bleeding, previous gastric surgery, or palpable mass) *(12)*. Only five individuals in this age group had "simple" dyspepsia without "sinister" symptoms, and all five already had lymph node metastases at the time of diagnosis. Early mortality was high in these five patients *(12)*.

ETIOLOGY

Helicobacter pylori

In their landmark publication in 1983, Warren and Marshall *(13)* characterized *H. pylori*, a curved Gram-negative rod, and described its relationship to histologic gastritis. Subsequently, the organism was shown to satisfy Koch's postulates as an infectious cause of gastritis and was linked to peptic ulcer disease and gastric cancer. It is now recognized to be the cause of most acute and recurrent ulcers. Acquisition of infection appears to occur in early childhood and, although the evidence is only indirect, transmission of *H. pylori* is presumably via fecal-oral or oral-oral routes. Consequently, this mechanism is felt to explain the high prevalence of infection in children in developing nations who live in conditions of less than optimum sanitation. On the other hand, in developed nations with better living conditions and public health measures, children are less frequently exposed to infection. For example, in a U.S. study, the prevalence increased from approximately 10% at age 20 years to approximately 50% at 60 years *(14)*.

The mechanism(s) by which *H. pylori* causes ulcer disease is not entirely clear. The organism does not invade the gastric mucosa, yet it induces an intense local and systemic host inflammatory response. This inflammation enhances mucosal susceptibility to acid injury. In addi-

tion, it disrupts the control of gastric acid secretion, leading in some patients to high acid and in others to low acid secretion. This disrupted secretory physiology, coupled with altered mucosal defense, leads to peptic ulcer disease *(15–17)*.

Early studies reported that *H. pylori* infection occurred in 90–95% of patients with duodenal ulcer and 70–90% of those with gastric ulcers *(18–22)*. However, more recent estimates suggest that the association between *H. pylori* and ulcer disease is somewhat lower, especially in the United States. A small single-center study from Rochester, NY evaluated patients with non-NSAID-related duodenal and/or gastric ulcers. Overall, *H. pylori* was identified in only 61% of patients with duodenal and/or gastric ulcers. The prevalence was even lower (52%) in nonminorities *(23)*. A large multicenter study of patients with non-NSAID-induced duodenal ulcers reported a 73% prevalence of *H. pylori (18)*. These more recent studies suggest that, at least in some areas of the United States, the prevalence of the organism in those with peptic ulcer is not as high as initially thought, and they call into question the recommendation for universal empiric antimicrobial therapy for all patients with duodenal ulcers without first documenting infection *(24)*.

Many ulcer patients who are infected with *H. pylori* concomitantly use NSAIDs *(25–27)*. *H. pylori* infection and NSAID use appear to be independent risk factors for the development of ulcers, but the effects of their interaction remain controversial. Some authors suggest that *H. pylori* may attenuate the ulcergenic effects of NSAIDs and that eradication may actually delay gastric ulcer healing *(28)*. Most, however, agree that infection and NSAIDs have additive or even synergistic effects on ulcer risk. Interestingly, the prevalence of infection in those with complicated ulcer disease, bleeding, or perforation is generally less that that seen with uncomplicated disease *(29,30)*. For example, in patients with bleeding ulcers, Jensen et al. *(31)* noted in previous Center for Ulcer Research and Education (CURE) trials that *H. pylori* prevalence was less than or equal to 75%, yet in their more recent study, *H. pylori* prevalence was 54.9% for bleeding duodenal ulcer and 53.2% for bleeding gastric ulcer. The reason for this lower prevalence and the actual fall in the prevalence of infection recently reported in complicated disease is not known, but factors such as NSAID use may be responsible. Nonetheless, *H. pylori* is still found in most patients with uncomplicated or complicated ulcers and plays a central role in the pathogenesis of this disease. Consequently, its diagnosis remains essential in the evaluation and treatment of peptic ulcer patients.

A number of national and international groups have published guidelines relating to the diagnosis of *H. pylori* infection *(32)*. All agree that

testing is appropriate in any patient with active or past duodenal or gastric ulcer, but they disagree on testing in other situations. The most suitable test depends on the clinical circumstances, especially if EGD is planned.

When endoscopy is not planned, a noninvasive test for *H. pylori* is the most appropriate. Several such tests are available, but serology is the most widely used. It tests for the presence of antibodies to one or several *H. pylori* antigens in whole blood or serum. The methodology is widely available, well accepted by patients and physicians, relatively inexpensive, and unaffected by medications such as proton pump inhibitors (PPIs) or antibiotics. The sensitivities of commercially available serologic tests vary somewhat but are approximately 90%; specificities are a bit less, approximately 85%. Because antibodies remain detectable long after infection is gone, serology is not suitable to document bacterial eradication following treatment *(33)*. On the same basis, patients who have spontaneous clearance of infection or clearance after treatment with antibiotics given for unrelated reasons can have false-positive blood tests. This is a particular problem when the background population prevalence of *H. pylori* is low. In areas of low prevalence (many regions of the United States have a prevalence of <25%), the positive predictive value of a positive blood test is reduced to levels that are unacceptable for clinical purposes, and most positive tests are false positive *(34)*. In such situations, consider one of the tests for active infection described below.

The urea breath test (UBT) is another noninvasive method to diagnose *H. pylori* infection. The organism produces the enzyme urease, which metabolizes urea to ammonia and CO_2. These in turn buffer the immediate surrounding acid milieu of the stomach, enabling it to survive. When *H. pylori* is present in the stomach, ingestion of carbon-labeled urea results in the production of labeled CO_2 that can be detected in the subject's breath sample. There are two forms of labeled urea: ^{14}C, a radioactive isotope, and the nonradioactive isotope ^{13}C. Although the amount of radioactivity in the ^{14}C-UBT is very small, the half-life is long and the long-term effects are unpredictable. Consequently the ^{13}C-UBT may be more ideal with regard to radiation issues *(35)*. However, the ^{13}C-UBT is more expensive and involves a test meal that makes it less simple than the ^{14}C-UBT. Overall, the performance of both types is similar, and they have a diagnostic sensitivity of more than 95% and a specificity of more than 90% *(35,36)*. As opposed to serologic testing, the UBT only detects active infection and is suitable to document eradication of *H. pylori* after treatment. Certain drugs affect UBT by reducing either the number of *H. pylori* organisms or their metabolic activity.

Recent use of antibiotics, bismuth compounds, and PPIs can cause false-negative test results for these reasons. Consequently, patients should not use PPIs for at least a week prior to breath testing. H2 antagonists generally do not reduce bacterial load and can be continued.

Appropriate clinical situations for which the UBT is ideal include documenting eradication of *H. pylori* after antimicrobial therapy when repeat endoscopy is not indicated (in patients who had complicated duodenal ulcer, for example) after antimicrobial therapy for MALT lymphoma, as an alternative to serologic testing in the young dyspeptic patient without alarm symptoms, and in the patient with a previous history of PUD. With regard to documenting eradication after antimicrobial therapy, a UBT is more reliable when it is performed at least 4 weeks after completing antibiotics, as advised in the American College of Gastroenterology guidelines for management of *H. pylori (37)*. Indications for documenting eradication in general include a history of complicated PUD (bleeding or perforation), MALT lymphoma, persistent or recurrent dyspeptic symptoms, and early gastric cancer *(37)*.

Another diagnostic method to detect *H. pylori* that has recently become available is stool testing. This is a capture antibody technique in which a polyclonal rabbit anti-*H. pylori* antibody is used to coat microtiter wells. *H. pylori* antigens from a stool sample are then captured and detected by conventional enzyme-linked immunosorbent assay (ELISA). It is a test of active infection and has sensitivities and specificities before and after treatment comparable to those of the breath test *(38)*. Like the UBT, stool test results can be affected by treatment with antibiotics, bismuth, or PPIs.

Endoscopic biopsies can also be used to detect *H. pylori*. A rapid urease test (RUT) takes advantage of the organism's urease enzyme. A biopsy specimen is placed either in a gel (CLO test, Ballard Medical Products) or on paper or membrane (HUT test, Astra Chemicals or Pyloritek Serim Research) containing urea and a pH indicator that changes color if the tissue sample contains the organism with its urease. The sensitivity and specificity of the RUTs are 95% and 98%, respectively *(39)*. As with the other tests that detect active *H. pylori* infection, treatment with PPIs or antibiotics can produce false-negative results. Patients should avoid these medications for at least a week before testing, especially when a RUT is the only biopsy test done *(39)*. Testing specimens from the gastric antrum alone is adequate in patients who have not been treated with PPIs or antibiotics. After treatment, however, the accuracy of RUT may be quite poor if only antral specimens are tested *(40)*. Therefore, testing in treated patients should include material

obtained from both the antrum and the body of the stomach to maximize diagnostic yield.

Actual histologic identification of *H. pylori* organisms represents an alternative endoscopic strategy and is considered the diagnostic gold standard. The sensitivity and specificity of histology approach 100%, especially when special stains such as silver stains are used *(41)*. However, this method obviously increases the cost, and false-positive and -negative results do occur, especially when tissue is examined by a less experienced histopathologist *(42)*. For a patient who has not received PPIs or antibiotic treatment, obtaining biopsies of the antrum for histology is adequate. However, in treated patients (as with RUT), antral histology alone may not detect organisms *(40,43)*. Examining additional biopsies obtained from the gastric body may improve diagnostic yield. For this reason the European *H. pylori* Study Group recommends that, after antibiotic therapy, two biopsies should be obtained from both the antrum and gastric body for histology and testing should be delayed to confirm eradication until at least 4 weeks after completion of treatment *(44)*.

In the setting of upper GI bleeding, biopsy for RUT and histology appears to have a lower sensitivity. For example, Tu and Lee *(45)* showed that in patients with a bleeding peptic ulcer the sensitivities of the CLO test and histology were 45.5 and 77.2% compared with 95 and 100% for breath testing and serology, respectively. Therefore, serology and UBT might be better diagnostic options in those with recent upper GI bleeding. However, PPIs are frequently prescribed for bleeding ulcers and could potentially alter breath test results. In addition, Laine and Cohen *(46)* have argued that if serology is used in a patient with a bleeding ulcer to diagnose *H. pylori* infection, its low specificity could lead to inappropriate management. Some patients would have false-positive serology results, thereby leading to unnecessary antibiotics and inappropriately obviating maintenance acid suppression to prevent a recurrent complication. They recommend that a RUT be used; if it is negative, then a banked biopsy specimen should be sent for histology *(46)*. There are no data on the use of *H. pylori* stool antigen testing in the setting of GI bleeding.

Other Causes

Gastrinoma (Zollinger-Ellison syndrome), infections such as syphilis and tuberculosis, opportunistic infections such as cytomegalovirus and herpes simplex virus in immunosuppressed patients, and Crohn's disease are rare causes of ulcers in the upper GI tract. Neoplasm must be considered in the appropriate patient with gastric ulcer. True "idiopathic" ulcers also occur. Some such lesions are thought to be heredi-

tary, since affected patients lack a common blood group antigen and gene. These ulcers are quite prone to complications, difficult to heal, and associated with abnormal gastric acid physiology and gastric emptying *(47,48)*.

TREATMENT

Acid suppression to promote mucosal healing, removing offending agents such as aspirin or NSAIDs *(49–60)*, and treating *H. pylori* if present are the principles of ulcer treatment. H2 receptor antagonists can heal peptic ulcers, but PPIs are more effective and are associated with higher and faster healing rates for both gastric and duodenal ulcers *(61–64)*. Most uncomplicated duodenal and gastric ulcers heal after once-daily dosing of PPIs for 4 and 8 weeks, respectively. Actually, in some duodenal ulcer patients with *H. pylori* infection, the duration of antisecretory therapy may be limited to the duration of the *H. pylori* regimen, which is commonly 2 weeks. Factors that may influence the decision to extend antisecretory therapy beyond 4–8 weeks include persistent symptoms, size of ulcer, presence of complicating factors such as bleeding, and potentially concomitant aspirin or NSAID use. Indeed, twice-daily PPI dosing for at least 8 weeks is appropriate to ensure healing of complicated duodenal and gastric ulcers.

Patients with peptic ulcers should be tested for *H. pylori*. Eradication of the organism has been shown to reduce the ulcer recurrence rate significantly. The 1-year recurrence rate of duodenal ulcers after successful eradication is generally reduced to less than 10%, compared with a recurrence rate of at least 50–60% if *H. pylori* persists *(65)*. Similar outcomes occur with gastric ulcers, with 1-year recurrence rates after successful eradication being less than 10% compared with 40–70% with persistence *(65)*. Eradication of the organism also prevents rebleeding from peptic ulcer disease, as shown in both short-term *(66–68)* and longer term studies, up to 4 years *(69)*. In fact, the reported rebleeding rate after eradication in these studies was 0%.

General principles for the treatment of *H. pylori* include multiple antibiotics and aggressive acid suppression, which improves efficacy of antimicrobials, in particular clarithromycin and amoxicillin. For example, the MACH 2 study showed that dual antimicrobial therapy in the absence of a PPI resulted in cure rates ranging only from 26–69%, compared with 87–94% when antibiotics were combined with PPIs *(70)*. Single antibiotic-based regimens have been abandoned in favor of dual antibiotic regimens due to higher eradication rates with the latter. The recommended duration of therapy remains controversial. In Europe, the

Table 1
14-Day Treatment Regimens for *H. pylori* Infection

PPI bid + A 1000 mg bid + C 500 mg bid
PPI bid + M 500 mg bid + C 500 mg bid
RBC 400 mg bid + A 1000 mg bid + C 500 mg bid
RBC 400 mg bid + M 500 mg bid + T 500 mg bid
BSS 525 mg qid + M 500 mg tid + T 500 mg qid + PPI bid
BSS 525 mg qid + M 250 mg qid + T 500 mg qid + H2RA

Abbreviations: PPI, proton pump inhibitor; A, amoxicillin; C, clarithromycin; M, metronidazole; RBC, ranitidine bismuth citrate; T, tetracycline; BSS, bismuth subsalicylate; H2RA, H2 receptor antagonist twice daily for 4 wk.

Adapted with permission from ref. *37*.

Maastricht Consensus report recommended 7-day treatment *(71)* whereas in the United States, 10–14-day therapy has been advocated and approved by the Food and Drug Administration *(72)*. Studies from the United States and Europe do suggest that both 10- and 14-day courses of PPIs with amoxicillin and clarithromycin are superior to 7-day treatment *(73,74)*. Several different regimens have been well studied and shown to have acceptable eradication rates.

When choosing a particular regimen, antibiotic resistance rates should be considered. Resistance to metronidazole approaches 100% in many developing nations due to its frequent use to treat parasitic infections; in the United States, such resistance ranges from 20 to 50% *(75)*. This resistance significantly impacts on the utility of metronidazole-containing regimens, especially 1-week triple therapies, and can reduce their efficacy by as much as 50% *(76)*. When metronidazole-resistant strains of *H. pylori* are treated with imidizole-based therapy for 2 weeks, the cure rate still drops, but remains approximately 70% *(65)*. Therefore, metronidizole is best reserved for those individuals allergic to penicillin or those failing initial treatment with macrolides. Resistance to clarithromycin in the United States is still low, ranging from 7 to 14% *(75)*, but when it is present it can reduce the efficacy of triple therapies to less than 50% *(76)*. Amoxicillin resistance is currently not a problem in the United States.

The American College of Gastroenterology in its practice guidelines recommended the five regimens listed in Table 1 as treatment options for *H. pylori (37)*. Although the bismuth four-drug therapies are least expensive, they have a greater rate of side effects and must be taken more frequently. As with any antibiotic regimen, the potential complication of *Clostridium difficile* infection exists with any of the options.

For those patients failing one treatment, an alternate regimen can be tried using a different combination, but quadruple therapy consisting of a PPI twice daily and bismuth-based triple therapy (Pepto-Bismol 2 tablets, tetracycline 500 mg, and metronidizole 500 mg all qid) given for 14 days has been recommended as the best second-line option *(65)*. A recent European study analyzed a new combination of antibiotics as "rescue" therapy following treatment failure with "triple therapy." In this study, a 10-day course of pantoprazole 40 mg bid., rifabutin 300 mg qd, and amoxicillin 1 g bid cured *H. pylori* in 89–100% of patients, with the lower rates occurring in those with either metronidazole- or clarithromycin-resistant strains *(77)*. This was significantly better than quadruple therapy with pantoprazole, bismuth, metronidazole, and tetracycline, although the dose of metronidazole was lower than customary (250 mg) and duration was only 10 days *(77)*.

For ulcer patients both infected with *H. pylori* and using an NSAID, the best strategy is acid suppression to heal the ulcer, eradication of *H. pylori*, and stopping the NSAID if possible to prevent ulcer recurrence. For healing NSAID-related ulcers irrespective of *H. pylori* infection, acid suppression with a PPI, such as omeprazole, is superior to misoprostol or an H2 blocker such as ranitidine *(26,27)*. Since some patients cannot easily discontinue NSAIDs, ulcer recurrence becomes an issue. PPIs are superior to H2 receptor antagonists and are better tolerated than misoprostol in preventing ulcer relapse for those continuing NSAIDs *(26,27)*. Maintenance treatment is not perfect, however. For example, during two recent studies evaluating primary and secondary NSAID ulcer prophylaxis, ulcers were prevented in only 61–72%, whereas a gastric ulcer recurred in 5–13% of those taking omeprazole during 6 months of follow up *(26,27)*. In addition, cure of *H. pylori* infection alone is insufficient to prevent recurrent ulcer complications in those who restart NSAIDs *(78)*. However, maintenance PPI can reduce recurrent ulcer complications if NSAIDs are required *(78)*.

Another option for ulcer patients requiring NSAIDs may be selective cyclooxygenase-2 (COX-2) inhibitors. Both celecoxib and rofecoxib are better analgesic and antiinflammatory medications than placebo or acetaminophen and have efficacy similar to that of nonselective NSAIDs such as diclofenac, ibuprofen, and naproxen *(79)*. These selective COX-2 inhibitors cause fewer endoscopic ulcers in the short term (3–6 months) than nonselective NSAIDs *(80,81)*. Furthermore, these drugs appear to cause fewer GI complications. In a large outcome study patients, with rheumatoid arthritis receiving rofecoxib for 6–12 months had fewer GI complications such as perforation, obstruction, upper GI bleeding, and symptomatic ulcers than those receiving naproxen.

The calculated number needed to treat with rofecoxib rather than naproxen to avert one clinical upper GI event in a 1-year period is 41 *(82)*. In another study, celecoxib caused significantly fewer GI complications compared with nonselective NSAIDs such as ibuprofen and diclofenac in patients with rheumatoid or osteoarthritis, except in those patients concomitantly taking low-dose aspirin *(83)*. Use of COX-2 inhibitors in the secondary prophylaxis setting is an attractive option that needs to be studied. Whether or not use of these selective agents will obviate maintenance acid suppression with PPIs, especially in individuals concomitantly taking low-dose aspirin, also remains to be seen (*see* Chap. 5).

BLEEDING

Peptic ulcer is the most common cause of acute upper GI bleeding and accounts for approximately 50% of all upper GI bleeding cases *(84)*. There are approximately 150,000 hospitalizations per year in the United States for evaluation and treatment of bleeding ulcers. Although hospitalization and surgery for uncomplicated ulcers have decreased in the United States and Europe over the past three decades, the number of hospitalizations for hemorrhage associated with ulcers has remained unchanged *(85)*. Even though ulcer bleeding stops spontaneously in at least 80% of patients, the overall mortality is also unchanged over the last 30 years, ranging from 6 to 7% in the United States *(85)* and averaging 14% in the United Kingdom *(86)*. Without specific hemostatic intervention, peptic ulcer bleeding continues or recurs in approximately 20% of patients *(87)*.

Ulcer bleeding starts when the ulcer base erodes into a blood vessel. Spontaneous hemostasis occurs when a sentinel clot (what is usually actually referred to as a "visible vessel") plugs the "side hole" in the vessel. The clot may then enlarge, remain attached for some time as it organizes, and eventually slough off, leaving the underlying vessel covered with a flat pigmented spot that fades to leave a clean ulcer base *(87)*. This process takes less than 72 hours, and rebleeding occurs if the clot undergoes lysis or falls off prematurely *(87)*.

Several clinical symptoms and signs relate to severity of bleeding and prognosis. Orthostatic hypotension suggests a 10–20% volume loss from the intravascular space, hypotension and resting tachycardia suggest at least 30% loss of blood volume, and the development of syncope can occur with rapid blood loss of as little as 10% volume *(88)*. Hematochezia in the setting of upper GI hemorrhage implies at least 1000 mL entering the upper GI tract *(89)*. This occurs in approximately 14% of upper GI bleeds, and the most common cause is duodenal ulcer *(90)*.

Table 2
Clinical and Endoscopic Poor Prognostic Indicators

Clinical indicators
Age > 60 yr
Severe comorbidities
Onset of bleeding during hospitalization
Emergency surgery
Clinical shock
Red blood emesis or NG aspirate
Requiring >5 U PRBCs
Endoscopic indicators
Major stigmata: active bleeding, visible vessel, adherent clot
Nonpigmented visible vessels
Size: ulcers >2 cm in diameter
Location: posterioinferior portion of duodenal bulb and high gastric on lesser curvature

Abbreviations: NG, nasogastric; PRBC, packed red blood cell.

Red hematemesis and concomitant hematochezia suggest massive brisk bleeding and are associated with a 30% mortality *(91)*.

Clinical and endoscopic prognostic indicators are shown in Table 2. With regard to age, the mortality of ulcer bleeding in those older than 60 years is 10%, compared with 0.5% in those 60 or younger *(85)*. The endoscopic appearance or "stigmata" of a bleeding ulcer also has prognostic value and is used to guide endoscopic therapy. The stigmata include a clean base ulcer associated with a very low risk of rebleeding on one end of the spectrum and an actively bleeding or spurting ulcer with highest risk of continued bleeding or rebleeding on the other end. The "visible vessel" is probably in most circumstances a misnomer since it represents instead a sentinel clot. Furthermore, its classic description as a "pigmented protuberance" requires elaboration because transparent or colorless protuberances may actually be higher risk lesions that are difficult to identify if they are not actively oozing *(87)*. Adherent clots and flat spots are self-explanatory. Endoscopic appearance does have prognostic value; the actively bleeding ulcer, the nonbleeding visible vessel, and the adherent clot all have a high risk of rebleeding, whereas the flat spot and clean base do not. The frequency of endoscopic stigmata, their rate of rebleeding if left untreated, and their associated mortality are outlined in Table 3.

An obvious priority of medical therapy for the patient with a bleeding peptic ulcer is volume and blood resuscitation. Surgical consultation should be considered early, in case medical therapy fails. There is no

Table 3
Endoscopic Stigmata and Outcomes

Stigmata	*Freq. (%)*	*Rebleed (%)*	*Mortality (%)*
Clean base	42	5	2
Flat spot	20	10	3
Adherent clot	17	22	7
Visible vessel	17	43	11
Active bleed	18	55	11

Adapted with permission from ref. *85*.

evidence that gastric lavage with fluid or ice-cold water prevents further bleeding, and most studies show that H2 blockers do not halt bleeding or reduce risk of rebleeding *(85)*. Nonetheless, these drugs do assist in healing of ulcers, and the risks of their use are minimal.

Data regarding the efficacy of PPIs are more encouraging. One recent double-blind, placebo-controlled study that evaluated high-dose omeprazole (40 mg bid) in patients with high-risk endoscopic stigmata who were not treated endoscopically showed that omeprazole significantly reduced rebleeding and the need for surgery *(92)*. Applicability to patients whose ulcers are treated endoscopically is unclear. PPIs are now available in intravenous form. In a recent randomized, double-blind, placebo-controlled study, intravenous omeprazole significantly reduced the risk of recurrent bleeding, transfusion requirement, and length of hospital stay in patients who underwent successful endoscopic hemostasis for bleeding ulcers with high-risk stigmata *(93)*. PPIs have not been shown to reduce mortality from peptic ulcer bleeding. Nonetheless, PPIs help heal ulcers quickly, and, given the recent studies showing benefits in those with peptic ulcer bleeding, their use (particularly in those with endoscopic signs indicating a high risk of rebleeding) is not unreasonable.

Endoscopy not only allows accurate diagnosis of ulcer bleeding but also provides potential therapeutic benefit. The decision to proceed with endoscopic hemostasis is usually based on the appearance of a lesion. Treatment is recommended for high-risk stigmata such as actively bleeding or oozing ulcers and nonbleeding visible vessels, whereas ulcers with flat red spots and clean bases have a low risk of rebleeding and do not benefit from endoscopic therapy *(85)*. Controversy exists regarding treatment of ulcers with an adherent clot that does not dislodge with aggressive washing. Options in such cases include observation versus

forcibly removing the clot with forceps or a snare and subsequently treating the underlying ulcer.

Traditional endoscopic methods of hemostasis include injection therapy and electrocoagulation. In general, prospective clinical studies show that both of these methods have similar efficacy *(85)*. Combination treatment is an attractive option because initial injection therapy could potentially control bleeding sufficiently to provide a clear endoscopic view of the ulcer and allow more accurate targeting and forceful tamponade with a thermal device. However, at least one study has failed to demonstrate added efficacy of dual treatment compared with single-modality therapy *(94)*.

Various agents have been used successfully with injection therapy including epinephrine, absolute ethanol, saline, and polidocanol. Each presumably exerts its effect primarily by causing local tamponade from the volume of injection itself. Electrical hemostasis using bipolar probes or thermal hemostasis with heater probes provides pressure tamponade and heat, which allow for thermal sealing of an underlying vessel. The use of lower power settings (15–25 W on BICAP II generators) with longer duration pulses (5–10 seconds) has been recommended as the best method to achieve hemostasis *(95,96)*. Newer devices have been used to treat bleeding peptic ulcers. Argon plasma coagulation is a noncontact diathermic technique that transmits ionized, electrically conductive argon gas that is brightly illuminated, visible, and generates heat. Power settings of 40–60 W at various flow rates up to 2.5 L/min often suffice, and small studies have demonstrated efficacy in controlling bleeding in peptic ulcers, but most published experience has been with nonpeptic causes of GI bleeding *(97)*. The maximal coagulation depth achieved by this method is 3–4 mm, which theoretically reduces the risk of perforation *(97)*. Another relatively new technique, the hemoclip, is a rotatable metallic device that essentially "staples" the vessel and surrounding tissue. Multiple clips are often deployed. Small studies have shown the hemoclip to be efficacious in achieving hemostasis in bleeding peptic ulcers with results comparable to other modalities *(97)*.

Although endoscopic treatment has led to clear reduction in rebleeding rates, most trials evaluating hemostatic therapy have not documented significant reduction in mortality *(85)*. Rebleeding after endoscopic therapy for major stigmata still occurs in as many as 20% of cases *(87)*. Risk factors for rebleeding after endoscopic therapy include ulcer location (ulcers located high on the lesser curve of the stomach or on the posterior or inferior portions of duodenal bulb probably caused by ero-

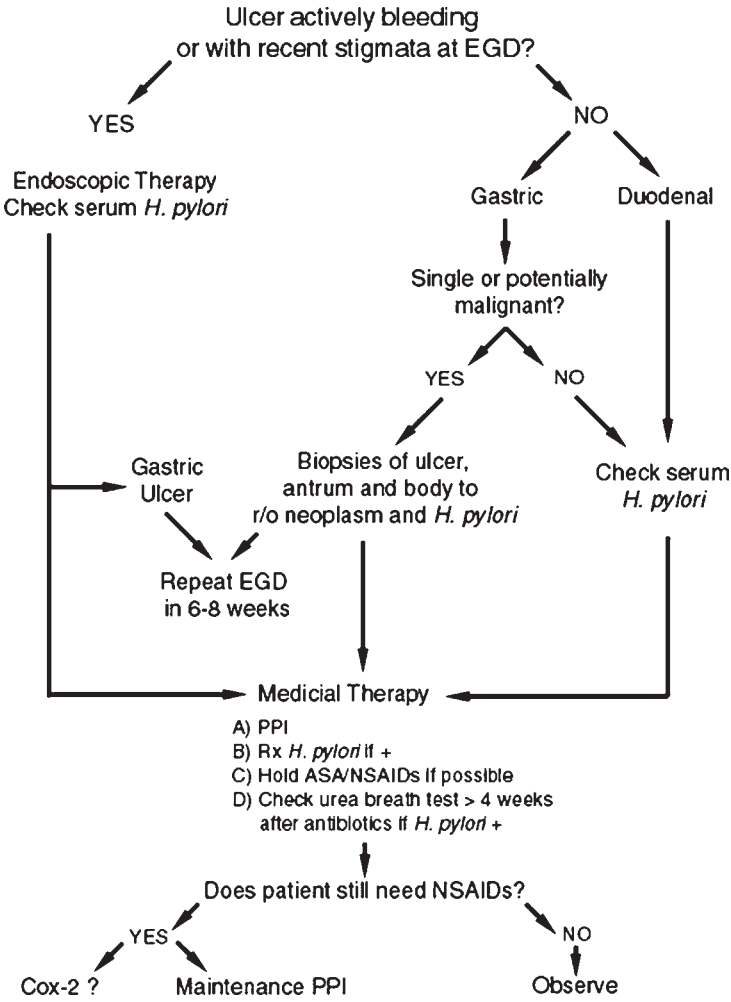

Fig. 1. Approach to the patient with bleeding peptic ulcer disease. ASA, acetylsalicylic acid; EGD, upper GI endoscopy; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor.

sion into the left gastric or gastroduodenal artery), large ulcer size, presence of comorbid illness, and older age *(87)*.

Early endoscopy in a patient with a bleeding peptic ulcer provides information that has a beneficial impact on hospital triage and cost of care. One potential management approach based on endoscopic findings suggests that patients with clean-based ulcers who have low risk of rebleeding could be safely discharged from the hospital within 1 day in the absence of severe anemia, old age, or comorbidities *(85)*. Those with

active bleeding or nonbleeding visible vessels, who are at highest risk, should be observed initially in the ICU and hospitalized for at least 3 days, whereas those with a clot or flat spot, who are at intermediate risk for rebleeding, could be hospitalized for observation in a non-ICU setting and discharged within 3 days *(85)*. A study of patients with bleeding non-NSAID ulcers confirmed that it is safe to discharge those with recent stigmata of hemorrhage after 3 days *(98)*. Another study evaluated elderly patients (65 years or older) including those taking NSAIDs and concluded that selective outpatient management of those with low-risk endoscopic findings and no major or minor clinical criteria for admission could be safely managed in the outpatient setting, which reduced the average cost of care by 63% *(99)*. Such results have obvious relevance in an era of cost containment.

SUMMARY

The most common cause of peptic ulcer is *H. pylori* infection. Peptic ulcer can present silently with complications such as hemorrhage, particularly in patients on NSAIDs. PPIs are the mainstays of therapy and should be held prior to noninvasive diagnostic tests for *H. pylori*. Effective eradication of *H. pylori* involves regimens utilizing multiple antibiotics. COX-2 inhibitors have lower incidence of causing peptic ulcers. Upper endoscopy effectively diagnoses peptic ulcers, reduces rebleeding, and allows for appropriate triage of patients with upper GI bleeding complications.

Figure 1 summarizes an algorithmic approach to bleeding peptic ulcer disease.

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4 Medical Therapy for Stress Ulcer Prophylaxis

When and With What?

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CONTENTS

INTRODUCTION

Patients admitted to intensive care units (ICUs) develop a spectrum of gastroduodenal lesions that may result in gastrointestinal (GI) bleeding. These range from superficial erosions to frank ulcers. It has been assumed that mucosal damage in these critically ill patients is related to "physiologic stress" (see below), hence the terms *stress ulcers* and *stress-related GI hemorrhage (1)*. These lesions most commonly occur in the proximal stomach [differentiating them from nonsteroidal

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Table 1
Determining the Impact of Prophylaxis for Stress-Related Gastrointestinal Hemorrhage: Stratification of Patients and Methodologic Quality Assessment

I. Population
   A. Setting: medical ICU, surgical ICU, respiratory ICU, neurosurgical ICU, burn unit
   B. Patient characteristics
      1. Type of risk: hypotension, severe respiratory insufficiency, sepsis, central nervous system injury, multiple trauma, major burns, acute hepatic failure, acute renal failure, coagulopathy, use of high-dose corticosteroids
      2. Magnitude of risk: number of risk factors, APACHE score (or similar)
      3. Mechanical ventilation (duration)
      4. Duration of ICU stay
II. Methodology: randomized, blinded, placebo-controlled
III. Outcomes
   A. Definition of bleeding: occult, overt, clinically significant
   B. Documentation of lesions and source of bleeding (endoscopically documented?)
   C. Mortality
   D. Nosocomial pneumonia (definition and documentation)

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

antiinflammatory drug (NSAID)-induced injury], but they may be found throughout the stomach and duodenum. During the past decade, prophylaxis of stress-related bleeding has been attempted, using a variety of agents [antacids, histamine 2 (H2) receptor antagonists, sucralfate, proton pump inhibitors], and has become routine in most hospitals throughout the world. The rationale for this approach is based on the assumption that stress-related GI hemorrhage is commonplace, on reports of reduction in the incidence of bleeding among patients receiving prophylactic agents, and on the (unproven) expectation that prophylaxis will reduce mortality. Routine prophylaxis for stress-related bleeding is expensive, however, and has potentially adverse consequences; also, the risk of clinically important bleeding appears to have decreased during the past decade independent of the use of prophylaxis *(2–5)*. The issue of what constitutes the most effective means of prophylaxis is also the subject of substantial debate *(6–9)*.

This ambiguity results from difficulties in interpreting a large but diverse body of literature. Populations studied and their magnitude of risk vary considerably and are often poorly defined. Definitions of bleeding also vary, and in many cases it is difficult to quantitate objectively

the degree of bleeding, which may range from occult blood in the nasogastric aspirate to that requiring transfusion. The source of bleeding is often not documented endoscopically. Most studies are not randomized or placebo-controlled. Metaanalyses have attempted to make sense of a heterogeneous group of studies, each of which individually has little power to provide an estimate of the effect of prophylaxis on bleeding *(7–9)*, but these analyses have also reached discordant conclusions. Consideration of the clinical significance of stress-related bleeding should rigorously define the population in question and the relationship of mucosal injury to bleeding and mortality *(1,2,6,7)* (Table 1).

IS ROUTINE PROPHYLAXIS FOR STRESS-RELATED GASTROINTESTINAL HEMORRHAGE INDICATED?

More than 3 million patients are admitted to ICUs in the United States each year. Although GI bleeding caused by stress ulceration is an important complication in critically ill patients, routine prophylaxis is indicated only if this is a common and clinically significant entity.

How common, then, is stress-related bleeding? Early descriptions of stress-related bleeding in burn patients and those subjected to severe trauma suggested that gastric mucosal lesions were common and often associated with severe life-threatening hemorrhage *(10,11)*. These studies, many dating back two decades, reported gastric erosions and ulcers in 85–100% of severely ill patients during their hospital course. Likewise, several endoscopic studies demonstrated a variety of mucosal changes ranging from nonhemorrhagic erosions and petechial lesions to ulcers in most critically ill patients early in their ICU stay *(10,12–14)*. Severe and clinically important hemorrhage was uncommon, however, in many of these studies. The incidence of actual bleeding from stress-related lesions has been inferred from numerous studies examining the efficacy of medical prophylaxis. These studies are heterogeneous in setting and definitions of bleeding (see above), and they report an incidence of stress-related hemorrhage that ranges widely, from 8 to 33%. Overall, studies comparing various agents with no treatment or placebo suggest that the incidence of stress-related bleeding in untreated ICU patients is approximately 16% *(1,6)*, with an incidence of serious bleeding episodes of 6–7%. This is in keeping with an observational study *(15)* that determined the incidence of stress-related bleeding in 174 untreated medical ICU patients to be 14% overall, with a 6% incidence of overt bleeding ("coffee-ground" emesis, hemetemesis, or melena). Few of these studies document the actual bleeding source endoscopically in the

patients in question, and many are more than a decade old. Since 1984, at least 18 English language publications have reported on the risk of stress-related hemorrhage in patients not given prophylaxis *(2,3,5,12, 15–27)* (Table 2). Some were observational studies, but most patients were reported as part of randomized trials of medical prophylaxis. Stress-related bleeding was low in most observational studies *(2,5,15, 22,23,25)* (0.4, 0.6, 1.5, 2, 6, and 25% in six studies). The risk of hemorrhage in control patients in clinical trials ranged widely, from 0 to 38% (median, 13%).

Recent studies suggest an even lower incidence of clinically important bleeding in ICU patients, possibly in part owing to more aggressive care in the modern ICU: better nutritional support, early treatment of infections, and maintenance of adequate tissue perfusion *(25,28)*. A more rigorous definition of what constitutes clinically important bleeding has also been a factor. In a recent observational study, Cook et al. *(2)* examined the risk factors for GI bleeding in more than 2000 critically ill patients entering the ICU (70% did not receive stress ulcer prophylaxis) and found the incidence of clinically important bleeding (hemodynamically significant bleeding or that requiring substantial blood transfusion) to be only 1.5%. Furthermore, clinically important bleeding occurred in only 0.1% of patients without respiratory failure or coagulopathy, whereas patients with one or both of these risk factors had a 3.7% incidence of hemorrhage. In a prospective cohort study, Zandstra and Stoutenbeck *(25)* reported important stress-related bleeding in only 1 of 167 patients (0.6%) during 2182 treatment days in the ICU. They attributed this low rate (despite no prophylaxis) to aggressive care including inotropes and vasodilators, selective decontamination of the digestive tract, and suppression of generalized inflammation with steroids. In a prospective randomized study Ben-Menachem et al. *(3)* randomized 300 medical ICU patients to continuous infusion of cimetidine or sucralfate or no treatment. Of 100 severely ill patients not receiving prophylaxis, 13 met criteria suggesting the possibility of clinically important GI hemorrhage. Stress-related lesions were found in only six of these patients at endoscopy, however, emphasizing the need for endoscopic documentation in such studies.

The low overall incidence of clinically important stress-related bleeding in the modern ICU suggests that not all patients entering such units require prophylaxis. Identifying patients at particularly high risk for bleeding and documenting the efficacy of prophylaxis in these patients is therefore important. In their analysis, Cook et al. *(2)* estimated that if prophylaxis reduces the risk of stress-related bleeding by 50%, one would need to administer prophylaxis to more than 900 low-risk patients

Table 2
Studies of Prophylaxis for Stress-Related Hemorrhage[a]

Author (reference)	*Year*	*Population*	*Placebo (no.)*	*Prophylaxis (no.)*	*Risk (%) of hemorrhage (95% CI)*[b]	*Absolute risk (%) reduction*[c]	*Relative risk reduction (95% CI)*[d]
Schuster et al. *(15)*	1984	Medical	179	Observational	6 (3–10)	—	—
Pinilla et al. *(20)*	1985	Surgical	61	65 Antacid	13 (6–24)	23	0.82 (0.32–2.13)
van den Berg et al. *(21)*	1985	Mixed (MV)	14	14 Cimet	7 (0.1–34)	0[e]	5 (0.67–37.5)
Peura et al. *(12)*	1985	Mixed	18	21 Cimet	38 (17–64)	Endos	—
Lacroix et al. *(16)*	1986	Pediatric	21	19 Cimet	38 (18–61)	0[e]	1.24 (0.6–2.56)
Groll et al. *(28a)*	1986	Mixed	107	114 Cimet	10 (5–17)	40	0.51 (0.2–1.34)
Karlstadt et al. *(17)*	1990	Mixed	33	54 Cimet	21 (9–39)	90	0.11 (0.01–0.83)
Reusser et al. *(18)*	1991	Neuro-surg	21	19 Ranit	0 (0–13)	0	—
Ruiz-Santana et al. *(19)*	1991	Mixed (MV)	30	43 Ranit/sucral	3 (0.1–17)	0[e]	2.16 (0.24–19.8)
Cook et al. *(5)*	1991	Mixed (MV)	100	Observational	2 (0–6.2)	—	—
Lacroix et al. *(22)*	1992	Pediatric	698	Observational	0.4 (0.1–1)	—	—
Cochran et al. *(23)*	1992	Pediatric	208	Observational	25 (19–31)	—	—
Martin et al. *(24)*	1993	Mixed	66	65 Cimet	33 (22–46)	50	0.42 (0.16–1.04)
Cook et al. *(2)*	1994	Mixed (all)	2252	Observational	1.5 (1–2)	—	—
		(low risk)			0.1 (0.01–0.5)	—	—
Ben-Menachem et al. *(3)*	1994	MICU (all)	100	200 Cimet/sucral	6 (2–13)	17	0.83 (0.26–2.64)
		(high risk)	65	148 Cimet/sucral	8 (3–17)	13	0.88 (0.31–2.47)
Zandstra et al. *(25)*	1994	Mixed	167	Observational	0.6 (0.01–0.9)	—	—
Chan et al. *(26)*	1995	Neuro-surg	49	52 Ranit	43 (30–55)	60	0.40 (0.21–0.79)
Burgess et al. *(27)*	1995	Neuro-surg	18	16 Ranit	28 (12–42)	100	0.02 (0.01–1.73)

Abbreviations: CI, confidence interval; Observational, no intervention/prophylaxis; (MV), all patients mechanically ventilated; Cimet, cimetidine; Endos, endoscopically defined outcomes; Neuro-surg, neurosurgical intensive care unit; Ranit, ranitidine; Sucral, sucralfate; MICU, medical intensive care unit. [a]Studies of prophylaxis for stress-related hemorrhage published in 1984 or later that included a placebo/no-prophylaxis group. Data reflect frequency and risk reduction for clinically important hemorrhage, if provided by authors. [b]Frequency of stress-related hemorrhage in placebo/no-prophylaxis groups (calculated exact 95% confidence intervals appear in parentheses). [c]Absolute risk reduction afforded by prophylaxis (efficacy). [d]Relative risk reducation owing to prophylaxis and corresponding 95% confidence intervals. [e]Frequency of stress-related hemorrhage is higher in patients receiving prophylaxis than in patients not receiving prophylaxis. Modified with permission from ref. *53*.

to prevent one episode of bleeding. On the other hand, only about 30 high-risk patients would have to receive prophylaxis to prevent an episode of clinically important bleeding.

WHICH PATIENTS ARE AT HIGH RISK FOR DEVELOPING STRESS-RELATED BLEEDING?

Few patients who enter the modern ICU will develop life-threatening stress-related bleeding (see above). Patients who do develop stress-related hemorrhage, however, may experience significant morbidity and mortality. It is therefore important to identify the subgroups of ICU patients who would benefit most from prophylaxis. Stress-related lesions have been described in a wide range of clinical settings including severe respiratory insufficiency, hypotension, sepsis, major burns, severe trauma, central nervous system injury, acute renal failure, acute hepatic failure, and coagulopathy. Most of these clinical situations are associated with alterations in the gastric microcirculation, which may lead to local hypoxia and ischemia, increased vascular permeability, critical tissue acidity, and reperfusion injury *(1)* (Fig. 1).

Several prospective cohort studies and randomized trials have correlated the incidence of stress-related bleeding with a variety of risk factors. Most concentrate on the number of risk factors (Table 1) or illness severity scores rather than the relative risk associated with individual variables. Most studies suggest that the risk of bleeding is low if fewer than two associated risk factors are present. Indeed, this has been the minimum requirement for entry into several studies *(27,29)*. Some studies suggest that illness severity scores correlate with the risk of bleeding *(30,31)*, but recent studies employing the Acute Physiology and Chronic Health Evaluation (APACHE) II scale have been unable to show a clear difference in score between those who bleed and those who do not *(2,3)*. The risk factor most commonly associated with stress-related hemorrhage is respiratory failure requiring prolonged mechanical ventilation *(2,3,28)*. In a large prospective randomized trial, Ben-Menachem et al. *(3)* found that patients with stress-related hemorrhage had significantly more risk factors than patients who did not bleed. Of these factors, only respiratory failure and high-dose corticosteroid use were associated with a statistically significant risk for stress-related hemorrhage. Likewise, Cook et al. *(2)* found respiratory failure (defined as the need for mechanical ventilation for at least 48 hours) to be the most potent risk factor for bleeding (odds ratio, 15.6). Another individual risk factor associated with bleeding in several studies is the presence of coagulopathy *(2,15)*. It is likely that risk factors such as respiratory failure and

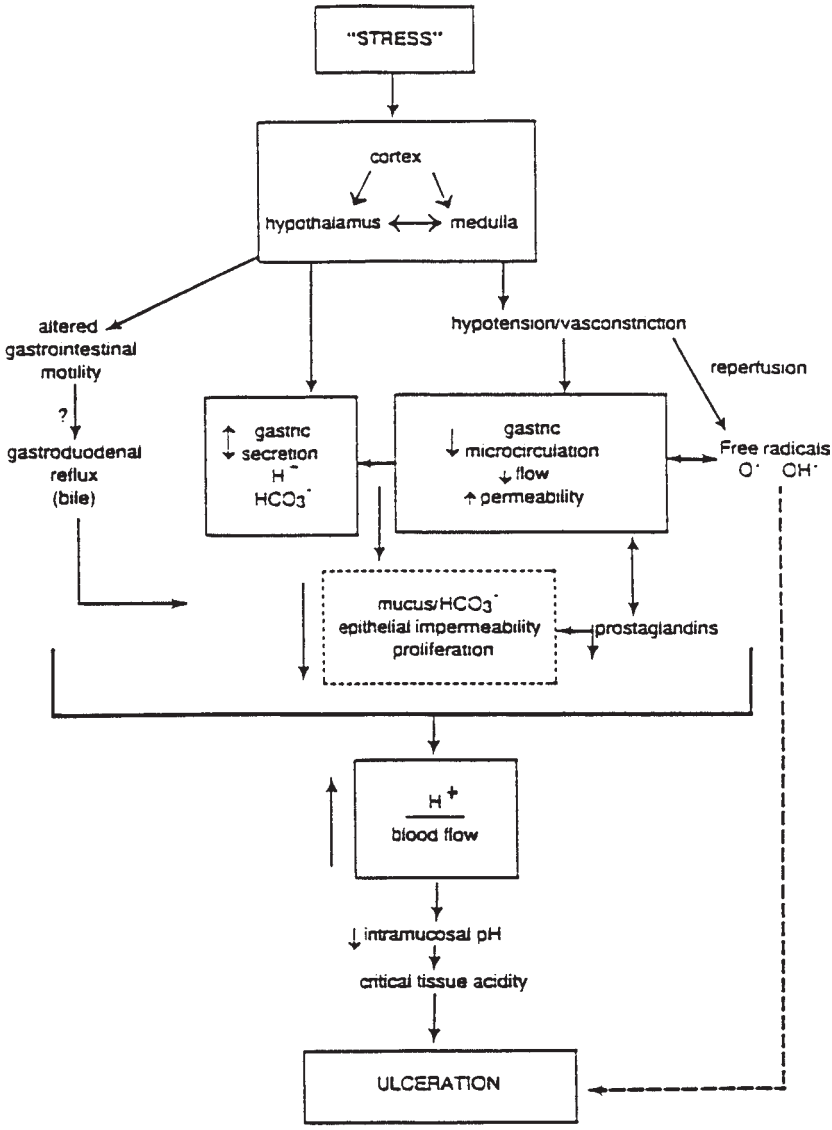

Fig. 1. Proposed mechanisms for development of stress-related mucosal damage. The specific relationships depicted are largely based on experimental findings, and remain somewhat speculative. (From ref. *1*, with permission.)

coagulopathy are important markers of severe illness that may predispose to stress-related bleeding.

Certain clinical settings such as severe trauma, head injury, and significant thermal injury appear to be especially associated with stress-

related bleeding, although these associations are largely based on older studies. In a recent analysis of 33,637 major trauma patients *(32)*, the overall incidence of clinical stress ulceration was low (although most received prophylaxis) but was independently associated with severity of injury according to an injury severity score (ISS ≥ 16) and spinal cord injury. Patients with nontraumatic neurosurgical lesions with low preoperative coma scores (Glasgow Coma Scale < 9) may also represent a subgroup with increased risk *(26,27)* compared with other neurosurgical patients.

IS MEDICAL PROPHYLAXIS FOR STRESS-RELATED GASTROINTESTINAL HEMORRHAGE EFFECTIVE?

Numerous randomized trials have suggested that the incidence of stress-related GI hemorrhage is lower in those receiving medical prophylaxis with antacids, intravenous H2 receptor antagonists, or sucralfate. Most include small numbers of patients, however, and many do not include no treatment or placebo groups. Furthermore, definitions of bleeding vary widely and include occult blood in nasogastric aspirates, overt GI bleeding of all types (hematemesis, bloody gastric aspirate, hematochezia), and "clinically important bleeding," often defined as overt bleeding accompanied by evidence of hemodynamic instability or a significant decrease in hemoglobin requiring transfusion. No individual study has definitively established whether prophylaxis significantly decreases clinically important bleeding, nor has one modality been shown to be clearly superior to another. Furthermore, although patients developing GI bleeding in the ICU setting have a high mortality rate, no study has determined that prophylaxis itself reduces mortality. Bleeding often occurs as a terminal event in the setting of multiorgan failure. Nevertheless, aggregate clinical trials suggest that stress-related GI bleeding may be reduced overall by 50% as the result of medical prophylaxis *(9)*.

Antacids were the first agents to be used for stress ulcer prophylaxis *(33–35)*. Bleeding was demonstrated to occur less frequently in those receiving antacids titrated to maintain an intraluminal gastric pH of 4 or more compared with no treatment. Many patients in these trials had microscopic or overt bleeding, but few had hemodynamically significant bleeding, and sources of bleeding were not documented. A recent metaanalysis *(7)* suggested a trend toward decreased overall bleeding when antacids are compared with no therapy [odds ratio (OR), 0.66; 95% confidence interval (CI) 0.37–1.17]. Although a beneficial effect on clinically important bleeding was also suggested, the sample size was too small to provide meaningful results.

Prophylaxis with H2 receptor antagonists or sucralfate has superseded the use of antacids for the most part in ICUs because of convenience of administration and also potential antacid-related side effects such as diarrhea and hypermagnesemia. Continuous infusion of H2 receptor antagonists provides more reliable and consistent control of gastric pH compared with bolus administration *(36)* and has been used in most recent studies. Cook and associates *(7)* recently reviewed 269 articles on stress ulcer prophylaxis and identified 63 relevant randomized trails for inclusion in a metaanalysis. They determined that H2 receptor antagonists and sucralfate both reduced overt stress-related bleeding compared with no prophylaxis. H2 receptor antagonists were also associated with lower clinically important bleeding compared with placebo or no therapy (common OR, 0.44; 95% CI 0.22–0.88). Sucralfate's effects on the incidence of clinically important bleeding were not distinguishable from those of antacids or H2 receptor antagonists, but only one trial compared sucralfate with no prophylaxis.

The results of metaanalyses may differ, however, from those of large randomized controlled trials *(37)*. A large prospective randomized controlled trial *(3)* compared the efficacy of continuous infusion cimetidine or sucralfate and no prophylaxis in 300 patients admitted to a medical ICU. Stress-related bleeding was documented by endoscopy in patients meeting criteria for substantial hemorrhage. Stress-related hemorrhage was observed in 6% of control participants and in 5% of those receiving sucralfate or cimetidine (relative risk compared with control, 0.83 for each group; 95% CI, 0.26–2.64; $p = 0.75$). The failure to show a benefit for prophylaxis was not owing to the degree of illness in the patients studied, since the mean APACHE II scores of the three groups ranged from 16 to 18, and one-third of the patients in each group had scores greater than 20. These authors concluded that routine prophylaxis was not warranted for patients entering medical ICUs.

Cook et al. *(38)* recently reported the results of a large (1200 patients) multicenter, randomized trial that compared sucralfate (1 g every 6 hours) with intravenous ranitidine (50 mg every 8 hours) for prophylaxis of stress-related GI bleeding. Clinically important bleeding was defined as overt bleeding (hemetemesis, nasogastric aspirate containing blood or "coffee-ground" material, melena, or hemotochezia) plus one of four significant hemodynamic events reflective of hemorrhage. All patients had APACHE II scores greater than 20 and required prolonged mechanical ventilation. Clinically important bleeding was relatively low in both groups but was significantly higher in the sucralfate group (3.8% sucralfate vs 1.7% ranitidine). Nonetheless, it is unclear whether stress-related bleeding *per se* was significantly different between those

receiving ranitidine and those receiving sucralfate. Only 17 of 33 patients with clinically important bleeding underwent endoscopy, and many of these patients had multiple types of findings (not all typical of stress-related lesions). Indeed, the source of bleeding was not well defined in at least 8 patients in the ranitidine group and 11 patients in the sucralfate group. Although the relative risk of bleeding in the ranitidine group versus the sucralfate group is similar if one includes only those with typical stress-related lesions (0.41), the difference is not statistically significant. Furthermore, because both groups received prophylaxis, the overall efficacy of prophylaxis for stress-related hemorrhage (compared with no prophylaxis) is unclear.

Proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole) are potent inhibitors of acid secretion by virtue of their specificity for the H^+/K^+ ATPase of the parietal cell (the proton pump) Intravenous omeprazole has been investigated for a number of clinical applications in Europe and Asia but is not available in the United States. An intravenous preparation of pantoprazole (Protonix I.V.™) has recently become available in this country. Some authors have used an alkalinized suspension of omeprazole or lansaprazole (simplified suspension formulations) administered orally or through nasogastric or gastrostomy tubes to suppress intragastric acidity. Two small open-label trials reported that none of the ICU patients requiring mechanical ventilation and with at least one risk factor for stress-related GI hemorrhage developed clinically important hemorrhage while receiving prophylaxis with omeprazole suspension *(39,40)*. In another trial that compared intravenous omeprazole with the H2 receptor antagonist ranitidine for prophylaxis of acute gastroduodenal bleeding after renal transplantation, no stress-related bleeding occurred in either group (one patient in the ranitidine group bled from a known duodenal ulcer) *(41)*. None of these studies included no treatment or placebo groups.

Studies utilizing intravenously administered proton pump inhibitors in the ICU setting are currently under way, but those specifically addressing stress-related bleeding have not yet been published. Most studies aimed at stress bleeding prophylaxis have targeted pH levels higher than 4.0 in hopes of preventing bleeding. The precise dose of intravenous protein pump inhibitor needed to achieve this level in the ICU needs to be determined. Studies that have addressed the issue of recurrent bleeding after endoscopic treatment of gastric and duodenal ulcers (not stress-related) have targeted a higher pH of 6.0. Lau et al. *(42)* recently demonstrated that intravenous omeprazole (80 mg bolus injection followed by continuous infusion of 8 mg/h) significantly reduced the risk of recurrent bleeding after endoscopic treatment of

bleeding ulcers compared with placebo. Rebleeding rates were 6.7% in the omeprazole group versus 22.5% in the placebo group. A similar study comparing intravenous pantoprazole with intravenous ranitidine is ongoing in the United States.

It has been suggested that selective decontamination of the digestive tract using oral and nonabsorbable antimicrobial agents as well as intravenous antibiotics might reduce the incidence of hospital-acquired infections, including pneumonia, in critically ill patients *(25)*. Cockerill et al. *(43)* reported that selective decontamination was associated with a lower incidence of bacteremia and pulmonary infection in ICU patients compared with no treatment. Total length of hospital and ICU stay and mortality were lower in the treatment group, but the differences were not statistically significant. There is little evidence that selective decontamination of the digestive tract has a major influence on the occurrence of stress-related bleeding *per se (28)*, and this cannot be recommended as routine treatment in ICU patients at this time.

Maintenance of adequate nutrition by parenteral or continuous enteral feeding may itself be associated with a reduced risk of stress-related bleeding in ICU patients *(19,44)*. Continuous enteral feeding via a nasogastric tube is associated, however, with an increased incidence of bacterial gastric colonization *(45)* and nosocomial pneumonia *(46)*.

IS PROPHYLAXIS FOR STRESS-RELATED GASTROINTESTINAL HEMORRHAGE SAFE?

The use of any therapy for stress ulcer prophylaxis can only be recommended if the benefits of intervention outweigh the risks. Medical prophylaxis should not be associated with substantial side effects. Most adverse reactions associated with antacids, H2 receptor antagonists, proton pump inhibitors, and sucralfate are mild and readily reversible on discontinuation of the medication. However, there have been reports of an increased frequency of nosocomial pneumonia associated with the use of antacids and H2 receptor antagonists *(47–50)* in the ICU setting. Alkalization of gastric contents may predispose to gastric colonization with Gram-negative organisms, retrograde oropharyngeal migration, and aspiration, leading to nosocomial pneumonia in mechanically ventilated patients. The overall incidence of nosocomial pneumonia in hospitalized patients is estimated to be 1% *(41)*, whereas the incidence in mechanically ventilated patients approaches 20% *(51)*. In Europe, nosocomial infection has been reported in 45% of patients occupying an ICU bed for more than 24 hours *(52)*. Twenty-one percent were ICU-

acquired infections, and pneumonia accounted for almost half of ICU infections reported. Stress ulcer prophylaxis was found to be a risk factor for pneumonia, and ICU-acquired pneumonia increased the risk of death (OR, 1.91; 95% CI, 1.6–2.29).

Prod'hom et al. *(50)* compared the incidence of nosocomial pneumonia in 244 mechanically ventilated patients receiving sucralfate, antacids, or ranitidine. There was no difference in early-onset pneumonia among the three groups. Among 213 patients observed for more than 4 days, however, pneumonia was observed in 5% of patients who received sucralfate compared with 16 and 21% of patients who received antacids or ranitidine, respectively. In their recent metaanalysis (see above) Cook et al. *(7)* reported that in comparison with no prophylaxis, H2 receptor antagonists are associated with an increased incidence of pneumonia (OR, 1.25; 95% CI 0.78–2.00). Sucralfate is associated with a lower incidence of nosocomial pneumonia compared with antacids (OR, 0.80; 95% CI 0.56–1.15) and H2 receptor antagonists (OR, 0.78; 95% CI, 0.60–1.01). Sucralfate is also associated with a reduced mortality rate relative to antacids and to H2 receptor antagonists (OR, 0.83; 95% CI, 0.63–1.09).

It should be noted, however, that not all studies have demonstrated an increased incidence of nosocomial pneumonia associated with use of H2 receptor antagonists compared with sucralfate, and one study *(3)* suggests that both H2 receptor antagonists and sucralfate may be associated with an increased incidence of nosocomial pneumonia compared with no prophylaxis. It must also be pointed out that nosocomial pneumonia has been poorly documented in many studies, and definitions of nosocomial pneumonia also vary greatly. Few studies rigorously define nosocomial pneumonia or employ protected brush specimens or bronchoalveolar lavage to improve diagnostic accuracy *(40)*. A recent large multicenter, randomized trial was designed to have the statistical power to detect a difference in the rates of pneumonia between those receiving ranitidine (50 mg bolus every 8 hours) and those receiving sucralfate (1 g every 6 hours). Rigorous clinical criteria were used to define ventilator-assisted pneumonia clinically, and patients in whom pneumonia was suspected on clinical grounds underwent bronchoalveolar lavage or protected brush-catheter sampling to confirm the diagnosis. No statistical difference was observed in the incidence of pneumonia between the two groups. This study does not rule out the possibility, however, that both agents may be associated with an increased risk of pneumonia, because a no treatment or double placebo group was not included.

COST CONSIDERATIONS

For prophylaxis to be recommended, the intervention should prevent an important clinical outcome (clinically significant bleeding, mortality), the benefits of intervention should outweigh the potential risks (nosocomial pneumonia in patients on prolonged mechanical ventilation), and the cost should not be prohibitive. Since most patients in the modern ICU do not appear to be at risk for clinically important bleeding, some authors have proposed limiting prophylaxis to ICU patients who are at high risk of developing stress-related hemorrhage. This would result in a decrease in overall cost. Others believe that all patients entering ICUs should receive prophylaxis since the benefits outweigh the risks, and the cost associated with some prophylactic agents is relatively small.

Cost of prophylaxis is determined not only by cost of the prophylactic agent (and its administration), but also by economic outcomes such as cost of treatment of stress-related hemorrhage (and the benefit of reduction by prophylaxis), and cost of treatment of adverse outcomes such as nosocomial pneumonia and adverse drug reactions. This can be measured as the marginal cost effectiveness, i.e., the additional cost of prophylaxis, minus any cost savings owing to the use of prophylaxis, divided by the number of bleeding episodes prevented, and translates into the cost per bleeding episode averted. Ben-Menachem et al. *(53)* recently performed such a cost effectiveness analysis for stress-related GI hemorrhage, emphasizing cost to the health care system. The marginal cost effectiveness of prophylaxis versus no prophylaxis was calculated separately for sucralfate and continuous infusion cimetidine assuming a 7-day ICU stay. Cost per bleed averted was calculated for different degrees of risk of stress-related hemorrhage and risk reduction by prophylaxis. The effect of nosocomial pneumonia on cost was also determined.

At the base-case assumptions of 6% risk of developing stress-related hemorrhage and 50% risk reduction owing to prophylaxis, the cost of sucralfate was $1144 per bleeding episode averted. Cost was highly dependent on the risk of hemorrhage and to a lesser extent on the efficacy of prophylaxis, ranging from a cost per bleeding episode averted of $103,725 for low-risk patients to cost savings for very high-risk patients. Cost increased significantly if the risk of pneumonia was included in the analysis, especially for populations at low risk of hemorrhage. Assuming equal efficacy, the cost per bleed averted of cimetidine was 6.5-fold greater than the cost of sucralfate. This study suggests that the cost of prophylaxis in patients at low risk of stress-

related hemorrhage is very high and adds substantially to health care costs. It emphasizes the need to determine the risk and severity of stress-related hemorrhage in specific ICU populations and the effect of prophylaxis on the risk of nosocomial pneumonia.

Maier et al. *(54)* calculated the cost of stress ulcer prophylaxis with continuous infusion intravenous ranitidine, taking into account cost of drug, pharmacy charges, and cost of administration in their ICU population and compared it with prophylaxis using sucralfate. They determined that use of sucralfate rather than H2 blockers would decrease annual costs in their ICUs by more than $30,000 per bed.

Such studies do not take into account the impact of stress-related hemorrhage on ICU length of stay. Those who develop stress-related bleeding might be expected to have a more prolonged ICU course. Prevention of hemorrhage would therefore make prophylaxis a more cost-effective strategy. It has not been proved, however, that the use of prophylaxis affects ICU length of stay. Moreover, studies addressing this issue suggest that the increased length of stay of patients with stress-related hemorrhage is not directly related to bleeding, but to overall clinical status.

These analyses suggest that sucralfate has an economic advantage over intravenous H2 receptor antagonists for use in the prophylaxis of stress-related hemorrhage. The impact of the reduced cost of generic H2 receptor antagonists has not yet been determined. This is likely to have a modest impact, however, since the cost of administration (I.V. solutions, pumps, and so forth) may not be reduced. The cost effectiveness of intravenous proton pump inhibitors in this setting also remains to be determined.

MEDICAL THERAPY FOR STRESS ULCER PROPHYLAXIS: WHEN AND WITH WHAT?

Despite a very large body of literature devoted to prophylaxis of stress-related GI hemorrhage, the answers to several questions remain unclear. This results, for the most part, from the heterogeneity of populations studied, the definitions of bleeding, and the questions asked. Nonetheless, the following answers and recommendations seem reasonable based on the available literature.

1. *Is routine prophylaxis for stress-related GI hemorrhage indicated in all patients entering the ICU?*

   Given the low overall incidence of stress-related bleeding in the modern ICU, routine prophylaxis of all patients is not justified. Most patients will not benefit from prophylaxis, and the cost of routine pro-

phylaxis in low-risk patients may be prohibitive. Furthermore, the potential increased risk of pulmonary complications associated with the use of some agents must be considered.

2. *Which patients should receive prophylaxis for stress-related hemorrhage?*

   ICU patients with fewer than two risk factors commonly associated with stress-related bleeding (Table 1), or with low risk scores for severity of disease [total risk score ≤ 10 *(30)*, APACHE II score less than 15] are at low risk for stress-related hemorrhage. In the absence of individual factors that may increase their risk substantially (prolonged mechanical ventilation, coagulopathy), prophylaxis is not indicated in these patients. Patients with at least two risk factors or multiorgan failure involving at least two organ systems (acute renal failure, acute hepatic failure, acute respiratory failure, hypotension, septic shock) should, on the other hand, receive prophylaxis.

   Patients who are expected to require prolonged mechanical for more than 48 hours and those with coagulopathy should received prophylaxis since these risk factors may substantially increase the risk of stress-related hemorrhage.

   Neurosurgical patients with a history of traumatic central nervous system injury (especially spinal cord injury), or nontraumatic neurosurgery patients with Glasgow Coma Scores less than 10 should receive prophylaxis.

   Patients with major trauma, especially those with an ISS of 16 or higher *(32)* should receive prophylaxis.

   Patients with thermal injury (especially those with burns involving >15% of the total body surface area) should receive prophylaxis.

   Patients requiring high-dose steroids (>250 mg of hydrocortisone or its equivalent per day) in the ICU setting should receive prophylaxis.

   Although most patients who enter medical ICUs or who undergo uncomplicated surgery will not benefit from stress ulcer prophylaxis, cases should be individualized according to the above criteria.

   These recommendations are meant to be somewhat liberal and need to be better defined in large prospective trials.

3. *What is the agent of choice for medical prophylaxis of stress-related hemorrhage?*

   The choice of pharmacologic agent for prophylaxis depends on considerations such as efficacy, side effects, cost, and ease of administration. Continuous infusion H2 receptor antagonists and sucralfate appear to have equal efficacy when they are used for prophylaxis of stress-related hemorrhage. Randomized, placebo-controlled trials are not yet available to determine the efficacy of proton pump inhibitors in this setting, but it is likely that they will be at least equally effective. Cost considerations and potential side effects (especially the risk for nosocomial pneumonia) favor the use of sucralfate at this point in time,

but the use of generic H2 receptor antagonists has become commonplace in many ICUs. Studies are ongoing to determine the efficacy, safety, and cost of intravenous proton pump inhibitors in this setting.

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5 Nonsteroidal Antiinflammatory Drug (NSAID)-Induced Gastropathy

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CONTENTS

INTRODUCTION

The term NSAID gastropathy refers to the spectrum of side effects in the upper gastrointestinal (GI) tract suffered by patients using nonsteroidal antiinflammatory drugs (NSAIDs). This toxicity includes commonly experienced "nuisance" symptoms such as dyspepsia as well as infrequent but much more serious events such as symptomatic and complicated ulcers. The incredible numbers of people taking NSAIDS, both prescription and over the counter, make this a significant health care issue. Since more than 70 million prescriptions and more than 30 billion nonprescription NSAIDS are sold yearly, NSAID gastropathy represents the most common serious adverse drug problem in the United States *(1)*.

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A large database of arthritis patients reveals that NSAID use is responsible for more than 103,000 hospitalizations and at least 16,500 deaths a year *(1)*. Among patients hospitalized for NSAID-associated bleeding, the mortality has been estimated at 5–10%, largely related to comorbid conditions. Prospective studies *(2,3)* have recently validated estimates that the risk of a serious event on NSAID therapy is 2–4% yearly. Nearly all patients who take aspirin and/or NSAIDs develop asymptomatic acute upper GI tract injury (ulcers and erosions) at some point in time. Interestingly, very few patients who develop serious complications have antecedent dyspeptic symptoms.

Endoscopic ulcers are used as an imperfect surrogate marker for clinically significant ulcers. A metaanalysis has evaluated the frequency of endoscopic ulcers in NSAID-using patients from medication prophylaxis trials *(4)*. The cohort of patients receiving aspirin or an NSAID for more than 4 weeks had a 9.1% incidence of gastric ulcers and a 4% incidence of duodenal ulcers. Low-risk patients are typically studied in such trials, and a higher prevalence of both gastric and duodenal damage has been observed in studies of arthritis patients. Gastric ulcers were seen in approximately 13%, whereas duodenal ulcers were observed in 11%; this represents a 46-fold increase for gastric ulcer risk and an 8-fold increase in duodenal ulcer risk, compared with the normal population *(5)*.

Increasing attention has been paid to the risk of ulcer complications experienced by patients on low-dose aspirin for cardiovascular indications. Aspirin at doses as low as 75 mg/d has been associated with significantly increased risk of bleeding gastric and duodenal ulcers *(6–8)*. The risk of upper GI bleeding with low-dose aspirin in these studies was increased approximately two- to fourfold, and enteric coating and buffering provided no protection. Doses of aspirin as low as 10 mg/d can cause ulcers *(9)*. This remains a relevant clinical concern for patients requiring an antiplatelet drug such as those using a cyclooxygenase-2 (COX-2)-specific inhibitor. Based on analysis of the large outcome study examining the safety of celecoxib [the Celecoxib Long-term Arthritis Safety Study (CLASS)], aspirin had a considerable adverse impact on the reduction in ulcer complications seen in patients taking celecoxib compared with traditional NSAIDs *(2)*.

PATHOGENESIS OF NSAID TOXICITY: ULCERATION

The complex elements that defend the gastroduodenal mucosa from damage are largely dependent on endogenous prostaglandins synthesized in the upper GI mucosa. COX is the rate-limiting catalytic step in prostaglandin production. At least two isoforms of COX have been

identified. COX-1 is constitutively expressed in the GI tract and plays an important role in the maintenance of normal gastric and duodenal physiology. COX-2 is an inducible form, which is upregulated in areas of injury *(10)*. However, COX-2 is also regulated in response to physiologic stimuli in numerous tissues, including the kidney, brain, and reproductive tract. NSAIDs, in general, nonspecifically inhibit COX isoforms, leading to both beneficial (antiinflammatory) and toxic (GI bleeding) outcomes.

The stomach and duodenum are covered by a mucus-bicarbonate barrier that provides a primary defense against the strongly acidic gastric lumen. Production of the components of this barrier is regulated by COX-1-derived prostaglandins. The surface epithelium provides the second line of gastroduodenal defense. Regeneration, the process by which larger epithelial defects (e.g., ulcers) heal, requires cellular proliferation, which is at least partly dependent on prostaglandins and growth factors *(11)*. Although very little COX-2 is present in the intact stomach, prostaglandins derived from COX-2 induced in the damaged stomach play an important role in ulcer healing, particularly related to angiogenesis stimulated by growth factors *(12)*. Another key factor preventing mucosal injury is maintenance of microvascular blood flow, which is also regulated by COX-1-derived prostaglandins.

The mechanisms by which NSAIDs cause ulcers remain incompletely understood; they involve both topical injury and systemic effects mediated by depletion of endogenous prostaglandins. Analogous to *Helicobacter pylori*-associated ulcer disease (large exposure risk with low absolute ulcer risk), the biologic basis for those individuals at increased risk for NSAID-related ulcers remains unknown.

Aspirin and most NSAIDs undergo ion trapping within the proximal GI mucosa, causing direct cellular injury. NSAIDs also directly attenuate the hydrophobic or nonwettable properties of the mucus barrier independently of prostaglandin-mediated actions *(13)*. Although topical effects can be largely prevented by administering enteric-coated NSAID formulations or prodrugs, the failure of these approaches to reduce the incidence of symptomatic NSAID-induced ulcers demonstrates that topical injury is not the critical determinant of NSAID-induced injury. For example, parenteral administration of an NSAID such as ketorolac may lead to ulcer complications *(14)*. Certain NSAIDs, such as indomethacin, piroxicam, oxaprozin, and ketorolac, also undergo an extensive enterohepatic recirculation, resulting in repeated exposure to the GI mucosa and increased toxicity *(11)*.

The clinically important adverse effects of NSAIDS—ulcers with an increased risk of complications—appear to be largely owing to their

systemic actions. Inhibition of COX-1, with a resultant decrease in endogenous prostaglandins critical to mucosal defense, is thought to be the most important mechanism of action. Platelet COX-1 is also inhibited irreversibly by aspirin and for as long as 18 hours by other NSAIDs. The impaired platelet function may potentiate GI bleeding from both the upper and lower GI tract.

COX-1 inhibition leads to not only quantitative but also qualitative decreases in mucus barrier function. Since prostaglandin deficiency impairs regenerative responses, erosions created by direct topical injury are exposed to acid in a vulnerable condition. Ulcerations occur in areas of decreased blood flow, and NSAIDs induce microvascular ischemia partly by causing neutrophil adherence in the microcirculation. The role of nitric oxide (NO) in the maintenance of epithelial integrity is related to its ability to maintain mucosal blood flow. In animal models, inhibition of NO synthesis exacerbates NSAID injury, and NO donors reduce NSAID toxicity *(15)*. NO-releasing aspirin/NSAIDs, which are not currently available in clinical practice, cause little damage despite marked inhibition of prostaglandin levels. This may be of greatest value when aspirin therapy is needed, allowing the utilization of a nonulcerogenic antiplatelet agent; clinical trials supporting the animal data are anxiously awaited.

Finally, acid plays an important secondary role in NSAID-induced ulceration. Recent data demonstrating the efficacy of high-dose H2 blockers and proton pump inhibitors in the treatment and prevention of NSAID damage support this concept. This suggests that topical injury is the first step in NSAID ulceration; then acid, in concert with prostaglandin depletion, synergizes for the development of clinically important ulceration. Finally, the discovery of two distinct COX isoforms has further illuminated the mechanisms of NSAID-induced injury. Traditional NSAIDs inhibit both isoforms of COX (dual inhibitors) and therefore produce both beneficial (antiinflammatory) and toxic (GI injury) effects, whereas the COX-2-specific inhibitors (COXIBs) appear to spare the GI mucosa from injury.

CLINICAL PRESENTATION: THE RISKS OF GASTROINTESTINAL COMPLICATIONS WITH NSAIDS

Until the recent outcome studies comparing the COX-2-specific inhibitors with traditional NSAIDs were completed, the only prospective data regarding the risk of serious complications caused by NSAIDs were from the Misoprostol Ulcer Complications Outcomes Safety

Assessment (MUCOSA) trial *(16)*, which studied the outcome of rheumatoid arthritis patients taking nonaspirin NSAIDs plus misoprostol or placebo. In the trial, 0.95% of patients on nonaspirin NSAIDs plus placebo developed serious GI complications within 6 months compared with 0.57% of patients on NSAIDs plus misoprostol. This is consistent with the frequently quoted 2–4% risk placed on the NSAID label by the Food and Drug Administration. The CLASS and Vioxx Gastrointestinal Outcomes Research (VIGOR) studies, comparing celecoxib and rofecoxib with traditional NSAIDs, confirmed these rates—approximately 2%/yr for complicated ulcers and 4% for symptomatic ulcers *(2,3)*.

Patients with a history of ulcer complications and those taking concomitant anticoagulant therapy have the highest risk of developing NSAID-associated serious GI complications. Moderate risk factors include advanced age, concomitant corticosteroid use, underlying major organ impairment, the use of high-dose or multiple NSAIDs, and arthritis-related disability. Gender and symptoms do not appear to predict increased risk *(17)*.

The past occurrence of an NSAID-associated serious GI complication is unequivocally associated with an increased likelihood (relative risk, 4.76) of another complication with recurrent NSAID use *(17)*. Not surprisingly, the concomitant use of NSAIDs and anticoagulants markedly exacerbates the risk of GI bleeding and increases the risk of hospitalization by 2.2-fold *(18)*. Although corticosteroids do not increase the risk of peptic ulcer disease when used alone, their use with NSAIDs leads to a nearly twofold increase in complication risk and a greater than tenfold risk of death *(19)*.

Increasing age is an independent predictor of experiencing an NSAID-associated GI complication. Clinically significant major organ impairment, particularly cardiovascular disease, was identified as an independent risk factor in the MUCOSA trial. Patients with cardiovascular disease were at a nearly twofold increased risk for GI complications caused by NSAID therapy, independent of aspirin use *(16)*.

Symptoms or the lack thereof, are not good predictors of NSAID complication risk. In one study, 58% of patients admitted with an NSAID complication had no antecedent dyspeptic symptoms, compared with the presence of symptoms in 75% of those with non-NSAID-complicated ulcers *(20)*.

A metaanalysis assessed the effect of different types and dosages of NSAIDs on serious GI complications, using ibuprofen as the reference medication. NSAIDs with increasing COX-1 activity were associated with increasing risks of serious GI complications. The relative risk was more than twofold higher with high- versus low-dose NSAID therapy.

The data indicated a trend for ibuprofen being less likely to cause serious GI complications than naproxen or indomethacin. This metaanalysis also concluded that the low occurrence of serious GI complications associated with ibuprofen in previous individual studies was probably owing to the low dosages of ibuprofen frequently used by patients *(21)*.

Several studies have evaluated agents that bypass gastric absorption (e.g., salsalate, nabumetone) or agents that are less potent COX-1 inhibitors (e.g., etodolac, nabumetone, and meloxicam). These trials demonstrated a significant reduction in endoscopic gastric ulcers and erosions with salsalate, etodolac, and nabumetone. Meloxicam and nabumetone have also been associated with a low rate of symptomatic ulcers in analyses of their respective clinical trial programs. However, the results of these studies should be interpreted cautiously for several reasons, including variability in the assessment of NSAID-associated endoscopic damage. Most importantly, these agents have not been subjected to large-scale outcome trials designed to examine the incidence of serious GI complications (e.g., bleeding, perforation, hospitalization, or death) *(5)*.

COX-2-Specific Inhibitors

Pharmacologists took advantage of subtle differences in the active sites of the two forms of COX to develop molecules (celecoxib, rofecoxib) that are highly selective inhibitors of COX-2. At doses employed in clinical practice, these agents do not affect COX-1 and thus are specific COX-2 inhibitors *(20)*. As would be predicted, these drugs, even at very high doses, spare GI prostaglandins. When studied with endoscopy, both celecoxib and rofecoxib produce rates of erosions nearly equivalent to placebo *(22,23)*. Rofecoxib has also been shown to be equivalent to placebo in fecal blood loss and intestinal permeability studies in humans. Clinical trials have demonstrated antiinflammatory efficacy of COX-2-specific inhibitors equivalent to that of commonly used NSAIDs in arthritis patients *(22)*. COX-2-specific inhibitors have been associated with low rates of serious GI complications in large clinical outcome trials, as discussed in detail below.

Helicobacter pylori *and NSAID-Induced Ulcers*

In the absence of NSAID use, *H. pylori* is accepted as the cause of most ulcers; its role in NSAID-associated ulcers remains controversial. The mechanisms of ulcer formation caused by NSAIDs and *H. pylori* are distinct: NSAID ulcers occur without gastritis (the endoscopic injury owing to NSAIDs occurs with little or no microscopic inflammation), whereas *H. pylori* ulcers occur in the setting of diffuse inflammation. The degree of inflammation is probably related to the virulence of the

H. pylori strain and host factors. Although NSAIDs decrease prostaglandin synthesis and *H. pylori* increases the synthesis of prostaglandins, there is little evidence that this provides protection from ulceration. Most importantly, it is clear from epidemiologic studies that *H. pylori* infection is not a required cofactor for NSAID-associated ulcers, since these ulcers may occur in the absence of *H. pylori (24)*. In patients who use NSAIDs chronically, the prevalence of *H. pylori* infection appears to be similar to those with or without ulcers *(25)*.

Whether eradication of *H. pylori* protects against NSAID-associated ulcers is another area of controversy. Although one study from Hong Kong found that NSAID-naïve patients who had successful *H. pylori* eradication had fewer ulcers, follow-up studies in non-NSAID-naïve patients failed to confirm these results, supporting the independence of these two ulcerogens *(26,27)*. These same investigators demonstrated that eradication of *H. pylori* alone was insufficient to prevent bleeding NSAID-ulcer recurrence in patients with a history of NSAID-associated ulcer bleeding *(28)*. In another arm of that study, eradication appeared as effective as omeprazole maintenance therapy for individuals taking low-dose aspirin for cardiovascular protection.

In summary, because *H. pylori* and NSAIDs appear to produce ulcers by different mechanisms, and in the absence of sound evidence suggesting a therapeutic advantage, testing for *H. pylori* does not appear to be indicated for all patients starting on NSAID therapy. Patients with a preexisting history of peptic ulcer disease should be tested for *H. pylori* and treated with antibiotics if the test is positive in order to reduce recurrence of *H. pylori*-associated ulcers.

PREVENTION AND TREATMENT OF DYSPEPSIA ASSOCIATED WITH NSAID USE

Dyspepsia and heartburn are common symptoms among patients who take NSAIDs. They occur daily in approximately 15% of those taking these medications. Within a 6-month period, 5–15% of rheumatoid arthritis patients discontinue a given NSAID because of dyspeptic side effects *(1)*. Symptoms lead to expenditures for administration of cotherapy with antiulcer medications and referrals for endoscopy. Symptom-driven costs are a substantial, albeit poorly quantified, component of the total cost of NSAID therapy.

In cross-sectional population-based studies, both aspirin and nonaspirin NSAID consumption was associated with a twofold increased risk of dyspepsia *(29)*. The cause of these symptoms is not known. Acid secretion is not increased in ulcer patients taking NSAIDs, and there is no evidence that NSAIDs effect esophageal clearance or

lower esophageal sphincter pressure *(30)*. However, since NSAID dyspepsia can be effectively reduced with acid suppression, gastroesophageal reflux may be implicated in certain patients.

Dyspepsia is seen with similar frequency in NSAID users with a normal upper endoscopy (19%) or minor endoscopic changes (9%) and in those with ulcer (30%) *(31)*. Patients who develop moderate or severe dyspepsia while undergoing treatment with antisecretory agents seem to be more likely to have endoscopic lesions. The results of controlled trials have shown a reduction in dyspeptic symptoms with antacids, H2 blockers, and proton pump inhibitors. Misoprostol does not reduce the frequency of dyspepsia. In clinical trials, dyspepsia is reported less frequently by patients taking COXIBs compared with those taking traditional NSAIDs but more often than those taking placebo *(22)*.

TREATMENT OF ULCERS IN NSAID USERS

When NSAIDs are continued, H2 receptor antagonists (H2RAs) have impaired effectiveness for healing ulcers compared with discontinuing NSAIDs. In a study of ulcer patients treated with ranitidine twice daily, those who continued NSAID use healed in 63% of cases at 8 weeks compared with 95% of those who had discontinued NSAIDs. Duodenal ulcers healed in 84% of patients continuing NSAIDs and healed in 100% of those who discontinued them *(32)*.

Proton pump inhibitors are superior to H2RAs and misoprostol for healing NSAID ulcers in the setting of continued NSAID use. In the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study, 541 patients with ulcers or extensive erosions were randomized to omeprazole 20 or 40 mg or ranitidine 150 mg twice daily. After 8 weeks of treatment, the rates of healing in all types of lesions were higher in those treated with omeprazole compared with ranitidine. The higher dose of the proton pump inhibitor was not superior to the lower dose *(33)*. Similar data exist for other proton pump inhibitors *(34)*. In the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study, in which 900 NSAID using patients with ulcers or extensive erosions were randomized to receive misoprostol 200 μg 4 times a day or omeprazole 20 or 40 mg once daily for 8 weeks, gastric ulcer healing was significantly more frequent on 20 mg of omeprazole compared with misoprostol. The healing rate on 40 mg of omeprazole was not significantly better than the lower dose. The rates of duodenal ulcer healing were also significantly higher in the groups given omeprazole 20 or 40 mg compared with misoprostol. Patients taking proton pump

inhibitors had improved quality of life and better control of dyspeptic symptoms compared with misoprostol *(35)*.

When the patient can discontinue the NSAID, all forms of antiulcer therapy work effectively. If the patient has a large or complicated ulcer, many clinicians use a proton pump inhibitor once or twice daily, based on evidence that larger ulcers heal faster with more potent acid suppression. In a patient with an uncomplicated NSAID ulcer who is able to discontinue the offending agent, any antiulcer therapy will be effective.

The standard of care remains that all patients with peptic ulcer disease, whether taking NSAIDs or not, undergo testing for and treatment of *H. pylori* infection. In the two previously mentioned large randomized trials (the OMNIUM and ASTRONAUT studies), the impact of *H. pylori* was evaluated in patients who continued NSAID therapy during treatment. Regression analysis demonstrated that *H. pylori*-infected patients taking acid-suppressive therapy had higher healing and lower recurrence rates of gastric and duodenal ulcers, an effect not seen in the placebo or misoprostol-treated patients. Although a number of hypotheses have been put forth for this observation, the most plausible appears to be that proton pump inhibitors are more effective acid inhibitors in the presence of *Helicobacter* infection *(36)*.

PREVENTION OF NSAID-ASSOCIATED GASTROINTESTINAL ULCERS AND COMPLICATIONS

Despite widespread NSAID use and the availability of protective agents, current medical evidence does not indicate a clearly superior strategy for reducing GI toxicity. At present, data from rigorously designed clinical and economic trials are not available to make accurate head-to-head comparisons between different strategies, including the use of the COXIBs.

Monitoring of the NSAID user should focus on vigilance for adverse GI symptoms (Fig. 1). All symptomatic patients should have a hemoccult examination and a complete blood count to evaluate for GI bleeding. NSAID users with hemoccult-positive stool usually have significant lesions when they are evaluated with endoscopy. If occult bleeding is detected, the patient should undergo esophagoduodenoscopy (EGD) to evaluate for an NSAID ulcer. A patient older than 50 years (or with other risk factors for colonic neoplasia, such as a positive family history) who has occult GI bleeding should also be considered for colonoscopy. Symptomatic low-risk patients without evidence of blood loss may switch to another NSAID (or COXIB) or receive treatment with antacids or H2RAs. Although acid inhibitors may relieve symptoms, they have not been proved to reduce GI complications, and it has been observed that some patients on such treatment may continue to be at risk for complications.

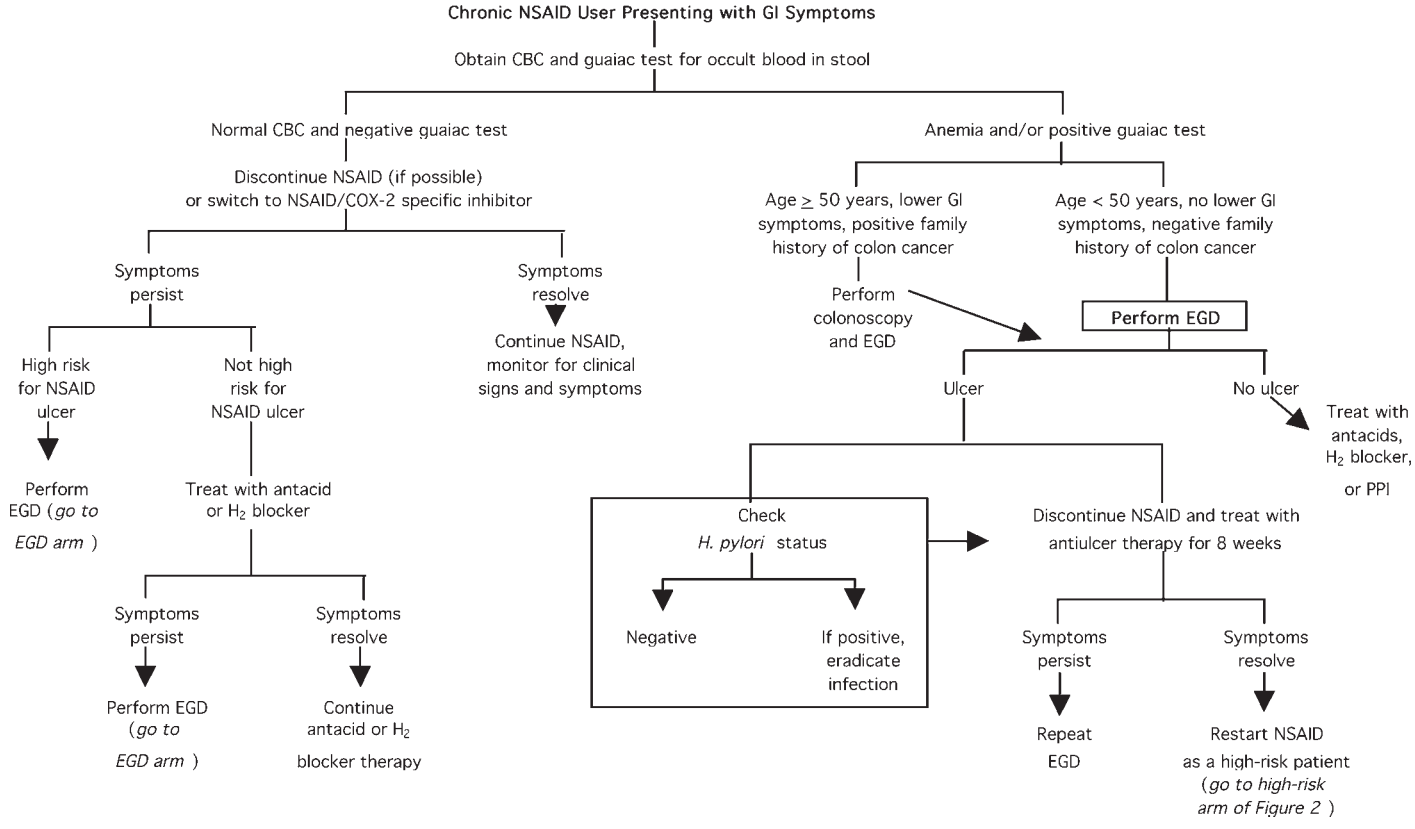

Fig. 1. Algorithm for the treatment of a patient using nonsteroidal antiinflammatory drugs (NSAIDS) and presenting with GI symptoms. CBC, complete blood count; COX-2, cyclooxygenase-2; EGD, esophagoduodenoscopy; PPI, proton pump inhibitor.

Misoprostol

Prostaglandin depletion is central to the development of NSAID ulcers; thus replacement therapy with a synthetic prostaglandin would be expected to reduce NSAID toxicity. Well-designed placebo-controlled studies *(37)* have demonstrated the efficacy of the prostaglandin E_1 (PGE_1) analog misoprostol for the prevention of endoscopic ulcers in NSAID-using arthritis patients. Misoprostol is the only agent currently available with well-established prophylactic efficacy for the prevention of NSAID-associated serious GI complications (e.g., bleeding, perforation, obstruction). The MUCOSA trial *(16)* identified a 40% relative risk reduction. Misoprostol cotherapy appears to be cost-effective in high-risk patients only. The number needed to treat is 264, that is, 264 chronic NSAID-using patients need to be treated for 6 months to prevent a single definite upper GI complication *(38)*. However, certain subgroups have an increased risk of serious upper GI complications, and the use of misoprostol would be more cost-effective and associated with a lower number needed to treat in these high-risk groups *(39)*. Those who benefited the most from misoprostol were patients with a previous history of GI bleeding (risk reduction, 50%), history of previous peptic ulcer disease (52% reduction), significant cardiovascular disease (38% reduction), and significant functional disability (87% reduction), as well as patients who required concomitant antacid use (48% reduction).

H2 Receptor Antagonists

The level of acid suppression provided by traditional doses of H2RAs does not prevent most NSAID ulcers, since only ulcer formation in the duodenum is significantly reduced. However, when H2RAs are given at double the traditional dose, they are effective at reducing gastric and duodenal ulcers *(40)*. There are no studies comparing high doses of H2 blockers with misoprostol or proton pump inhibitors for the prevention of NSAID ulcers.

Proton Pump Inhibitors

Given that high-dose acid suppression with H2RAs prevents NSAID ulcers in the stomach and duodenum, it follows that more potent proton pump inhibitors should be more effective. Omeprazole has proved effective in primary prophylaxis of NSAID-induced ulcers compared with placebo in a study of 169 patients requiring continuous NSAID therapy *(41)*. After 6 months, 78% of the omeprazole group remained in remission, compared with 53% in the placebo group ($p = 0.004$). There were three gastric ulcers and no duodenal ulcers in the omeprazole group, compared with eight and three, respectively, in the placebo group *(35)*.

In the ASTRONAUT study *(33)*, patients requiring continuous NSAID therapy were randomized, following ulcer healing, to receive ranitidine (150 mg bid) or omeprazole 20 mg daily. Gastric ulcers recurred in 5.2% of the omeprazole-treated patients versus 16.3% of those in the ranitidine-treated group ($p < 0.001$). For duodenal ulcers, there was a 0.5% versus a 4.2% ($p = 0.02$) rate of recurrence in the two groups, respectively. The OMNIUM study *(39)* compared omeprazole 20 mg once daily, misoprostol 200 μg twice daily, and placebo during 6 months of follow-up. In this study, 32% of patients taking placebo developed a gastric ulcer at relapse compared with 10% in the misoprostol group and 13% in the omeprazole group. Duodenal ulcers developed in 12% of those given placebos, 10% of those given misoprostol, and 3% of those given omeprazole. Omeprazole was not superior in reducing erosions. Omeprazole was superior in the maintenance of overall remission, largely because of its ability to improve NSAID-associated dyspepsia and overall quality of life. In a recent trial evaluating the prevention of endoscopic ulcers in *H. pylori*-negative NSAID users with a past history of ulcers, lansoprazole 15 and 30 mg was compared with misoprostol 200 μg qid *(42)*. In this study, both doses of the proton pump inhibitor were superior to placebo and had similar efficacy to misoprostol, but with fewer side effects.

There are no data to prove that cotherapy with a high-dose H2RA or a proton pump inhibitor reduces serious GI complications from NSAIDs. The MUCOSA trial suggests that one can extrapolate, albeit poorly, from reduction of endoscopic ulcers to serious GI complications. At this point, one can conclude that the reduction of endoscopic ulcers is largely equivalent between the two agents and that acid suppression tends to be superior in reducing ulcers in the duodenum. Cotherapeutic use of antisecretory drugs may still be associated with continued NSAID-associated risk for complications. In the maintenance phase of the ASTRONAUT study, there was a single GI complication, and it happened to be a patient on omeprazole. Thus, even though omeprazole was superior to both H2RAs and misoprostol, patients remain at risk for serious GI complications.

Safer Antiinflammatories: The COX-2-Specific Inhibitors

The ulcer risk associated with Celecoxib has been evaluated by endoscopy in patients with osteoarthritis and rheumatoid arthritis in studies lasting 3–6 months. In a 3-month study of patients with osteo- and rheumatoid arthritis, celecoxib 200 mg bid caused fewer endoscopic ulcers than naproxen 500 bid and ibuprofen 800 tid. There was no difference in the incidence of endoscopic ulcers compared with

diclofenac 75 mg bid *(22)*. A recent report compared the incidence of endoscopic ulcers in rheumatoid arthritis patients taking celecoxib, traditional NSAIDs, and placebo *(43)*. The inclusion of a placebo group is critical in these types of studies, since ulcers may occur in patients without use of antiinflammatory drugs, a consideration frequently overlooked. In this trial, the incidence of upper GI tract ulcers was 4/99 (4%) in the placebo group, 9/148 (6%) on celecoxib 100 mg bid, 6/145 (4%) on 200 mg bid, 8/130 (8%) on 400 mg bid, and 36/137 (26%) on naproxen 500 mg bid. The ulcer rates on celecoxib were not significantly different from those on placebo but were significantly less than naproxen.

Two 6-month, placebo-controlled, endoscopy studies have been performed with rofecoxib 25 and 50 mg compared with ibuprofen 800 mg 3 times daily. The study design included a baseline endoscopy and endoscopies at 6, 12, and 24 weeks. In the two studies, a total of 1517 patients were randomized. In one study of 742 patients, at 12 weeks 7.3% of patients on placebo developed an endoscopic ulcer, compared with 4.7% on 25 mg of rofecoxib, 8.1% on 50 mg of rofecoxib, and 28.5% in the ibuprofen group *(44)*. The incidence of 5-mm lesions was similar in these two studies. In a second study of identical design, similar safety with rofecoxib was observed.

When the two studies were combined, the incidence of endoscopic ulcers met predefined criteria for equivalence to placebo *(23)*. In an analysis of predictors of gastroduodenal ulcer development, the presence of erosions at baseline endoscopy, prior history of ulcer disease, age more than 65 years, and the presence of *H. pylori* were significant risk factors. However, analyses have demonstrated that *H. pylori* did not synergize with rofecoxib to increase the incidence of endoscopic lesions *(45)*. Similar observations have been made for the lack of effect of *H. pylori* and aspirin on endoscopic ulcers for patients on celecoxib, specifically, no increase compared with either risk factor alone *(46)*.

A relationship between endoscopic injury and serious GI complication rates cannot be directly demonstrated *(1)*. The rofecoxib clinical trials have examined the incidence of clinical ulcers, the so-called perforation, ulcer, and bleed (PUB) rate over 12 months, evaluating over 5000 patients. The COXIB was associated with a relative risk reduction of 0.51 *(47)*, representing a rate of 1.33 per 100 patient-years on rofecoxib compared with 2.60 on traditional NSAIDS. Most importantly, the incidence of clinically significant GI bleeding was also markedly reduced. In an analysis of the celecoxib clinical trials, the annualized incidence of upper GI complications on celecoxib was 0.20% compared with 1.68% on NSAIDs *(48)*.

To confirm long-term safety with both agents and support a clinically important risk reduction in serious GI toxicity, both manufacturers

performed long-term safety trials with the COXIBs. In the VIGOR trial, the safety of rofecoxib 50 mg was studied in comparison with naproxen 500 mg bid in over 7000 patients treated worldwide over 6–12 months *(3)*. The primary and secondary end points of this study were the occurrence of symptomatic and complicated upper GI events. The results of the trial are shown in Table 1. The COXIB was associated with a 50–60% reduction in ulcers, bleeding, or both.

In the celecoxib outcomes study (CLASS), 8000 patients worldwide with osteo- (90%) and rheumatoid arthritis (10%) were randomized to celecoxib 400 mg bid, ibuprofen 800 mg tid, or diclofenac 75 mg bid in a study of 6–12 months' duration *(2)*. In this trial the primary end point was the development of complicated upper GI events, with symptomatic ulcer development as the secondary end point. The primary end point in all patients was not met in the CLASS trial (Table 2), probably because of the inclusion of low-dose aspirin (Table 3). When information from the entire 12 months of the trial became available, the primary end point of the trial was not met even when those taking aspirin were excluded, probably reflecting numerous methodologic problems with the design of the trial as well as the high dropout rate *(49)*. These studies also demonstrated that those patients receiving COX-2-specific inhibitors who have a need for an antiplatelet agent must also take low-dose aspirin *(50)* and that these doses of aspirin will reduce the COXIB protection from ulceration (Tables 2 and 3).

Key components of the overall cost of disease management with NSAIDs are physician visits, medication expenditure, and endoscopies related to the development of GI side effects such as dyspepsia. COXIBs appear to cause fewer nuisance GI side effects than traditional NSAIDs, although side effects are more frequent than with placebo. Rofecoxib was noted to cause significantly fewer GI symptoms and less need for GI medication cotherapy in clinical trials of up to 6 months' duration. In general, the incidence of these adverse events and rates of antiinflammatory drug discontinuation were intermediate between traditional NSAIDs and placebo. A recent analysis confirmed that patients on rofecoxib underwent fewer GI-related procedures compared with the NSAID group (1.25% vs. 1.98%, $p = 0.057$ and had a reduced likelihood of adverse GI experiences. The risk reduction for rofecoxib compared with NSAIDs was 0.42 ($p < 0.01$) *(50)*.

Although analyses of clinical trials cannot be directly extrapolated to clinical practice, one may anticipate that the frequency with which patient symptoms require cotherapy and/or further evaluation with endoscopy may be reduced with rofecoxib and other COX-2-specific inhibitors.

Table 1
Rofecoxib GI Outcomes Study[a]

Event	*Rofecoxib* (n = *4047*)	*Naproxen* (n = *4029*)	*Relative risk (%) (95% CI)*	*Relative risk reduction (%)*	p *value*
Clinical UGI event	2.1	4.5	0.46 (0.33–0.64)	54	<0.001
Complicated UGI event	0.6	1.4	0.43 (0.24–0.78)	57	0.005
Any GI bleeding	1.2	3.0	0.38 (0.25–0.57)	62	<0.001

Abbreviation: UGI, upper gastrointestinal.
[a]Rofecoxib significantly decreased the incidence of all GI end points: rates per 100 patient-years.

Table 2
Celecoxib GI Outcomes Study for All Patients[a]

Event	*Celecoxib* (n = *3995*)	*Diclofenac/ Ibuprofen* (n = *3987*)	*Relative risk reduction (%)*	p *value*
Complicated ulcers	0.8	1.5	47	0.09
Complicated + symptomatic ulcers	2.0	3.5	43	0.03

[a]All patient rates per 100 patient-years (6-month data).

Table 3
Celecoxib GI Outcomes Study for Non-Aspirin Users[a]

Event	*Celecoxib* (n = *3995*)	*Diclofenac/ Ibuprofen* (n = *3987*)	*Relative risk reduction (%)*	p *value*
Complicated ulcers	0.5	1.3	62	0.04
Complicated + symptomatic ulcers	1.4	3.0	53	0.02

[a]Non-aspirin user rates per 100 patient-years (6-month data).

Since this class of agents appears to be as effective but safer than traditional NSAIDs, such agents represent a logical alternative to branded NSAIDs on the basis of both clinical and economic considerations (Fig. 2), particularly if the NSAID is given with another medication such as an H2RA or proton pump inhibitor. Patients with a history of ulcer complications and concomitant anticoagulant therapy have the highest risk of developing NSAID-associated serious GI complications. These patients would be expected to derive the greatest overall benefit from the reduced GI risk associated with COXIBs. Moderate risk factors include advanced age, corticosteroid use, chronic major organ impairment (particularly cardiovascular disease), and the use of high-dose or multiple NSAIDs, including aspirin. Use in these above-average risk patients is likely to be cost-effective, particularly if more than one of these risk factors is present *(51)*. More economic benefits will be achieved if additional medications are not required or if adequate symptom control occurs with the addition of a low-cost generic antisecretory drug to COXIB therapy.

Management of the patient requiring low-dose aspirin (Fig. 3) is more complex. Testing for and treatment of *H. pylori* may prove beneficial in these patients, as discussed previously. In high-risk patients,

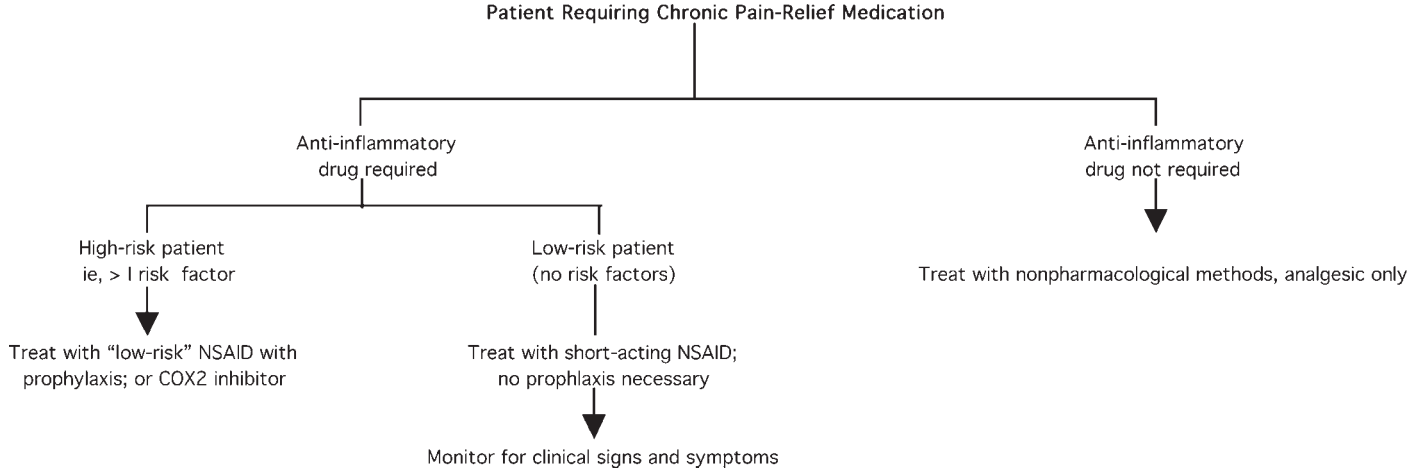

Fig. 2. Algorithm for the treatment of a patient who requires chronic pain relief medication. For abbreviations, see Fig. 1 legend.

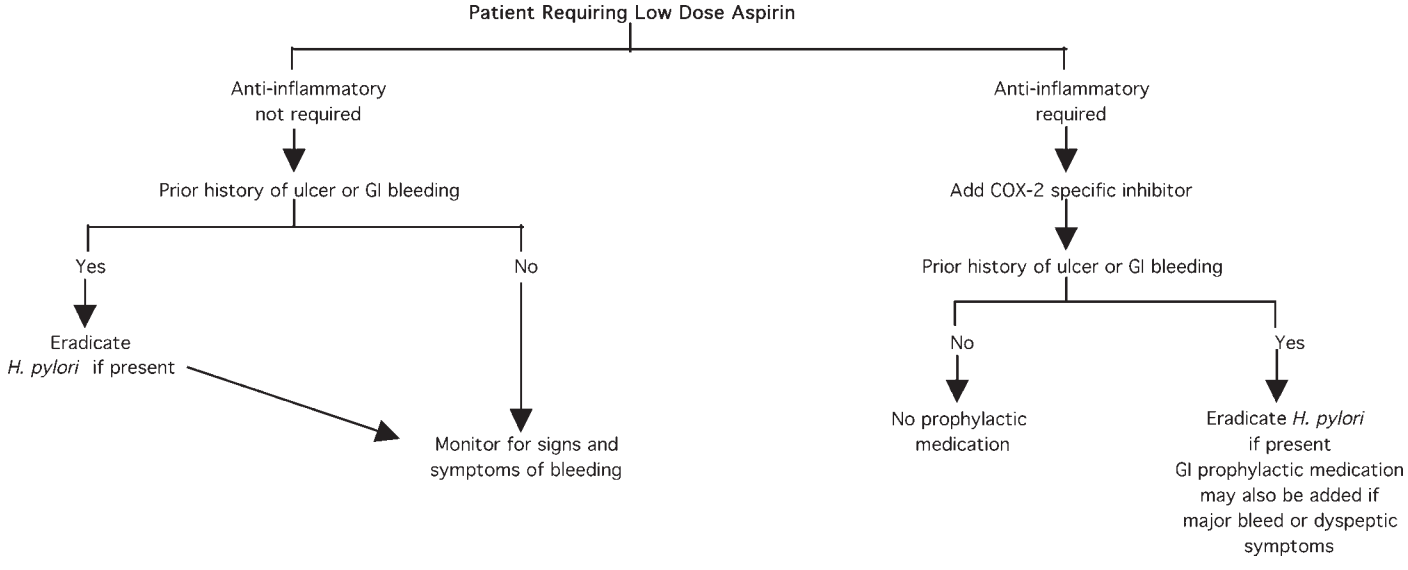

Fig. 3. Algorithm for the treatment of a patient who requires low-dose aspirin. COX-2, cyclooxygenase-2.

the aspirin therapy may mandate cotherapy to prevent bleeding. For those requiring antiinflammatory therapy, the use of a COXIB instead of a traditional NSAID to avoid the moderate additive risk seen in the CLASS study may be advisable for those with underlying risk factors.

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6 Portal Hypertensive Acute Gastrointestinal Bleeding

Thomas W. Faust, MD
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CONTENTS

INTRODUCTION

Gastrointestinal (GI) hemorrhage from portal hypertension is the most ominous form of bleeding. It carries the highest mortality, ranging from 30 to 40% and has an equally high rate of recurrence *(1)*. Vascular collaterals in the stomach, esophagus, small bowel, and colon form as a consequence of portal hypertension, and these vessels have a high risk of rupture. The vascular congestion can also lead to mucosal bleeding throughout the GI tract from portal hypertensive gastropathy, enteropathy, and colopathy.

Varices frequently complicate end-stage liver disease. More than 30% of compensated cirrhotic and 60% of decompensated cirrhotic

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patients have varices at the time of diagnosis *(2)*. Therefore, a comprehensive approach to diagnosis and treatment of portal hypertensive lesions such as esophagogastric varices and portal hypertensive gastropathy is essential to minimize patient morbidity and mortality.

The purpose of this chapter is to review important concepts pertaining to portal hypertension and bleeding complications. First, a brief overview of the anatomy of the portal venous system is presented. Second, important aspects of the history and physical exam that should alert the primary care physician to portal hypertension are described. The remaining sections focus on pharmacologic, endoscopic, radiologic, and surgical approaches to the prevention and treatment of portal hypertensive bleeding. Specific treatments for the management of bleeding esophageal varices are emphasized. Prevention of recurrent portal hypertensive bleeding and complications that may arise as a consequence of bleeding are also addressed.

ANATOMY OF THE PORTAL VENOUS SYSTEM

The superior mesenteric vein (SMV), splenic vein (SV), and coronary or left gastric vein drain into the portal vein. Venous drainage from the stomach, small intestine, pancreas, spleen, and colon passes through the main portal vein to the liver. Portal blood is rich in oxygen, vitamins, and amino acids that are derived from intestinal absorption *(3)*. These constituents contain multiple substrates for the liver's diverse metabolic and synthetic functions. The healthy liver is responsible for filtering portal venous blood before its return to the systemic circulation via the main hepatic vein and inferior vena cava.

PHYSIOLOGY OF PORTAL HYPERTENSION

Portal hypertension is defined as an elevation of the hepatic venous to systemic pressure gradient over the normal value of 3–6 mmHg. Portal hypertension arises as a consequence of either hepatobiliary or perihepatic vascular disease, which leads to increased resistance to flow in the portal vein. Secondary changes in vascular tone within the splanchnic and systemic circulations lead to increased blood volume and potentiate the portal hypertension.

Prehepatic, intrahepatic, and posthepatic diseases can give rise to portal hypertension. The initial increase in pressure is thought to develop as a result of sinusoidal compression by regenerative nodules and collagen deposition by fibroblasts *(4)*. Mechanical compression is potentiated by changes in vascular tone within the liver sinusoids. Increased collagen deposition in the space of Disse impairs oxygen delivery to

hepatocytes, increases sinusoidal vascular resistance, and correlates with the degree of portal hypertension *(5)*. These mechanical changes are potentiated by alterations in the hepatic microcirculation. Stellate cells transform into myofibroblasts in the perisinusoid and perivenular spaces within the liver. These cells exhibit increased vasoconstrictive properties during acute or chronic liver injury *(5)*.

The architectural changes in the liver are compounded by changes in the splanchnic and systemic circulation, which together increase portal blood volume and are responsible for up to 40% of the increase in portal blood pressure *(6)*. Models of end-stage liver disease show higher levels of vasodilating substances such as nitric oxide (NO) and prostacyclin in the systemic circulation and a decrease in these substances in the hepatic sinusoids. This vasoactive imbalance leads to systemic vasodilation and increased portal blood flow with simultaneous constriction of the intrahepatic vasculature *(1)*.

Esophageal and gastric varices arise as a consequence of increased portal blood flow and increased resistance to blood flow. Collateral blood vessels that surround the lower esophagus and stomach become engorged as a consequence of increased portal blood flow and the higher resistance to flow through the liver.

CAUSES OF PORTAL HYPERTENSION

Prehepatic Causes

There are several examples of prehepatic causes of portal hypertension. Most describe a mechanical incursion on the portal vein. Damage to the portal vein can occur as a consequence of malignant vascular invasion by hepatocellular carcinoma or secondary to most forms of chronic liver disease. Hypercoagulable states, collagen vascular disease, and oral contraceptive use are associated with portal vein thrombosis *(5)*. Chronic pancreatitis is associated with splenic vein thrombosis and prehepatic portal hypertension. Congenital arterioportal fistulae with arterialization of the portal vein and increased vascular resistance can also cause portal hypertension. Additionally, there are several reports of myeloproliferative diseases presenting with portal vein thrombosis *(7)*.

Intrahepatic Causes

Intrahepatic inflammation or structural changes in the liver can lead to portal hypertension through injury of portal venules, hepatic venules, or liver sinusoids. The fibrotic changes in the hepatic lobule in the setting of chronic viral hepatitis or alcoholic liver disease are the most common causes of portal hypertension. Inflammation of the liver from

Table 1
Causes of Portal Hypertension

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Splenomegaly
Intrahepatic
Chronic viral hepatitis
Alcoholic liver disease
Primary biliary cirrhosis
Malignancy
Acute and fulminant viral hepatitis
Peliosis hepatis
Wilson's disease
Schistosomiasis
Nodular regenerative hyperplasia
Posthepatic
Inferior vena cava thrombosis
Hepatic vein thrombosis
Cardiac failure
Constrictive pericarditis

infection such as acute viral hepatitis may also raise vascular resistance sufficiently to cause portal hypertension in the absence of the systemic hemodynamic changes seen in cirrhosis. In primary biliary cirrhosis (PBC), bile duct inflammation and damage to adjacent portal venule can lead to increased vascular resistance before cirrhosis occurs *(5)*. Refer to Table 1 for other intrahepatic causes of portal hypertension.

Posthepatic Causes

Posthepatic increases in vascular resistance from hepatic vein thrombosis (Budd-Chiari syndrome), inferior vena cava thrombosis, right heart failure, and constrictive pericarditis can lead to portal hypertension. Vascular congestion over time can result in cardiac cirrhosis with the associated systemic vascular changes that potentiate the portal hypertension.

DIAGNOSIS OF PORTAL HYPERTENSION

The diagnosis of portal hypertension can usually be made based on a carefully performed history and physical examination in conjunction with appropriate laboratory studies. Measurement of the hepatic venous

pressure gradient with an intravascular balloon occlusion catheter is seldom required but can be useful when there are few other clinical signs of liver injury.

Some authors have advocated measurement of the hepatic venous pressure gradient to assess adequacy of pharmacologic therapy for portal hypertension *(8)*. As most cirrhotic patients are at significant risk for complications from angiographic procedures, this practice has not been widely adopted.

History

A patient with portal hypertensive bleeding from varices or mucosal congestion may present with hematemesis, melena, hematochezia, or any combination of the above. In the evaluation of a patient with GI bleeding, the following historical features should increase the physician's concern that portal hypertension may be present. A history of excessive alcohol intake or chronic viral hepatitis should be noted. Additionally, any history of chronic parenchymal liver disease or cholangiopathy such as autoimmune hepatitis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, primary sclerosing cholangitis (PSC), or PBC raises concern that symptoms of bleeding may be caused by portal hypertension. A history of hypercoagulability or intraabdominal malignancy should prompt concern for vascular thrombosis or malignant infiltration with concomitant portal hypertension. Extrahepatic processes such as cardiac failure can lead through congestion to cardiac cirrhosis. Chronic pancreatitis with fibrotic encasement and thrombosis of the splenic vein commonly causes portal hypertension.

Specific features of the GI bleeding such as brisk hematemesis, profuse hematochezia, presyncopal symptoms, or syncope, when present, increase the likelihood of a portal hypertensive cause of hemorrhage.

Physical Findings

The important physical findings in a patient with portal hypertensive bleeding are stigmata of chronic liver disease such as jaundice, ascites, splenomegaly, spider angiomata, peripheral edema, and vascular collaterals on the abdominal wall (caput medusa). GI bleeding can also precipitate hepatic encephalopathy in patients with decompensated liver disease. Orthostatic hypotension suggests that approximately one-third of the blood volume has been lost and raises concern for portal hypertensive bleeding *(8)*. Most portal hypertensive lesions such as esophageal or gastric varices can cause massive and recurrent bleeding.

Laboratory Evaluation

Laboratory measurements that should raise concern for portal hypertension include abnormal liver chemistries and other serum markers of chronic liver disease. Elevated aminotransferases signal hepatocellular injury, but there is no correlation between the degree of transaminase elevation and the severity of histologic injury. Cholestatic liver chemistries (increased alkaline phosphatase, GGT) may reflect chronic biliary obstruction from PBC or PSC. Hypoalbuminemia and elevated prothrombin time suggest possible decreased hepatic synthetic function. Thrombocytopenia is commonly found in patients with portal hypertension, splenomegaly, and platelet sequestration. An abdominal ultrasound examination that demonstrates a large-diameter portal vein in combination with a platelet count of 140,000/mm^3 or less is a sensitive predictor of portal hypertension *(5)*.

APPROACH TO THE PATIENT WITH PORTAL HYPERTENSIVE BLEEDING

Resuscitation

A patient with variceal hemorrhage requires immediate stabilization. The intensive care unit is the optimal place to manage an actively bleeding patient. Vascular access with two large-bore intravenous catheters is the first step. Resuscitation with normal saline to restore circulating blood volume should begin as soon as access is attained. Coagulopathy should be corrected with fresh frozen plasma, vitamin K, and platelet transfusions, if required. Packed red blood cells should be transfused to preserve oxygen-carrying capacity and to restore the hematocrit to a range of 27–30%. Excessive transfusion may worsen portal hypertension and increase the risk of recurrent bleeding. It has been proposed that the portocollateral vasoactive response to volume loss, the presence of blood in the gut lumen, and volume resuscitation combine to increase splanchnic blood flow and portal hypertension *(9)*.

Pharmacotherapy

Pharmacologic efforts to treat variceal bleeding have focused on diminishing portal blood pressure by shunting blood away from the mesentery through the use of smooth muscle constrictors. Vasopressin, the posterior pituitary hormone, causes splanchnic vasoconstriction and was one of the first such agents used for this purpose. Intravenous infusion causes decreased portal blood pressure with an increase in systemic arterial pressure and a decrease in heart rate. Terlipressin is a long-acting analog of vasopressin that also reduces portal blood flow

through splanchnic vasoconstriction. It has a slightly better safety profile and can be dosed at 4–6-hour intervals rather than by continuous infusion. In randomized controlled trials, vasopressin provided marginal benefit in the control of bleeding but did not produce a survival advantage *(10)*. For both agents, because the vasoconstriction is nonspecific, mesenteric or cardiac ischemia can occur.

Nitrate preparations have been studied in portal hypertension. By causing venodilation, nitrates reduce systemic blood pressure and mildly decrease portal blood pressure. The effect of nitrates was found to be inadequate to allow their use as monotherapy for portal hypertensive bleeding. However, in studies that combined nitrates with vasopressin, bleeding control was improved and toxicity was less compared with vasopressin alone *(8)*.

The addition of the endogenous peptide somatostatin and its synthetic analog, octreotide has been regarded as an important advance in the treatment of portal hypertensive bleeding. Octreotide is thought to have three principal mechanisms in variceal bleeding. It blocks the increase in hepatic venous pressure and azygous flow after feeding *(11)*. It causes splanchnic vasoconstriction and downregulation of enteric secretion and motility. It blocks endogenous mesenteric vasodilators. Although octreotide's observed effect on portal blood flow in models of variceal hemorrhage has been variable *(12)*, the medication's low toxicity profile has made it a popular empiric choice for suspected portal hypertensive bleeding. In trials of acute variceal bleeding, it was more effective than H2 blockade and at least as effective as vasopressin but with fewer adverse effects *(13)*.

Although metaanalyses of randomized trials of octreotide have not shown a mortality benefit in portal hypertensive hemorrhage *(13)*, and it is not approved for treatment of variceal hemorrhage, a recent metaanalysis found octreotide to be superior to vasopressin/terlipressin or endoscopic therapy alone for sustained control of bleeding. Additionally, the complication rate from octreotide was comparable to that of placebo or no intervention *(12)*. Another study found that intravenous octreotide was as effective as endoscopic sclerotherapy for initial control of bleeding from esophageal varices. The raw data in this study favored sclerotherapy, but the differences between the two treatment groups were not statistically significant. The authors cite a trend toward better outcomes for patients treated with sclerotherapy *(14)*.

Endoscopic Therapy

Endoscopic therapy can be lifesaving for a patient with variceal bleeding, but in order for urgent upper endoscopy to have the greatest benefit,

it should be performed in an intensive care unit after adequate volume resuscitation. Endotracheal intubation with mechanical ventilation should be considered in any patient with active hematemesis or a decreased level of consciousness in order to protect the airway and to minimize the chance of aspiration.

The mainstay of endoscopic therapy for bleeding varices in the esophagus is injectable vascular sclerosants. There are several types of sclerosants: morrhuate, tetradecyl sulfate, and ethanolamine are three examples. They can be injected intravariceally or paravariceally. Sclerosants produce hemostasis by injuring endothelium and provoking variceal thrombosis and through a pressure effect from thrombus formation in an adjacent blood vessel *(15)*. Total obliteration of varices usually requires three to six endoscopic sessions. Sclerotherapy can be complicated by chest pain, fever, pleural effusion, and dysphagia. Esophageal ulceration with late stricture formation, perforation, and bacteremia are other possible sequelae *(16)*.

A comparison of several types of sclerosants in a canine model of variceal hemorrhage found that cyanoacrylate, tetradecyl sulfate, and polidocanol were most effective for reducing variceal size. Cyanoacrylate injections arrested bleeding more quickly. Epinephrine was shown to be more effective when injected around areas of secondary bleeding caused by the sclerotherapy needle *(17)*. When the hemorrhage is too profuse to allow adequate visualization, blind injections in a four-quadrant manner extending proximally from the gastroesophageal junction may be required.

More recently, endoscopic variceal ligation (EVL) has emerged as an effective treatment for esophageal varices. Using a transparent cylinder attached to the end of the endoscope, a varix is suctioned into the cylinder, and a rubber band is deployed around the varix, causing hemostasis, thrombosis, and sloughing of the variceal column. EVL may be technically more difficult in an actively bleeding patient because visualization of the varix is recommended before suction is applied.

In a comparison of EVL and sclerotherapy for treatment of active bleeding in cirrhotic patients, EVL was more successful for control of spurting varices. Bleeding ceased for at least 3 days in 97% of the EVL patients but in only 76% of the sclerotherapy patients. In the same study, EVL patients also required fewer blood transfusions and had fewer complications (5% vs. 29%) and lower mortality than patients treated with sclerotherapy *(18)*. In a recent randomized, controlled trial, EVL alone was compared with EVL with adjuvant sclerotherapy of varices that were too small to be eradicated by banding. Although complication rates and recurrent bleeding rates were similar between the two groups,

the patients who received adjuvant sclerotherapy had a significantly lower rate of variceal recurrence. At 1 year, the likelihood of variceal recurrence was 45% among patients who received only EVL and 24% for those who also received EVL followed by sclerotherapy *(19)*. These studies suggest that optimal results may be seen from a combination of endoscopic therapies to control bleeding and sequentially eradicate varices to prevent rebleeding.

When esophageal varices show endoscopic stigmata of recent hemorrhage, or when there is a high clinical suspicion that variceal bleeding is responsible for the patient's hemorrhage, endoscopic variceal ligation should be performed at 1–2-week intervals until the varices are obliterated. Follow-up endoscopy would be performed every 3–6 months thereafter to rule out variceal recurrence.

EVL has replaced sclerotherapy as the standard endoscopic treatment to prevent rebleeding because EVL obliterates varices in fewer treatment sessions with a lower rate of rebleeding and lower mortality *(20)*. A Japanese study that compared EVL with sclerotherapy for treatment of variceal bleeding in 101 patients found that hemostasis could be achieved in all patients of both treatment groups and that obliteration was approximately 90% in both groups. However, the rate of rebleeding was 40% in the sclerotherapy group and only 29% in the EVL patients. On average, EVL treatments were completed in 2.1 sessions versus 3.7 sessions for sclerotherapy. The most common complications, rebleeding and intramural hematomas, were seen less frequently in patients who received EVL *(21)*.

Active bleeding from gastric varices or portal hypertensive gastropathy is difficult to treat endoscopically. However, active bleeding from nonesophageal lesions may be addressed with surgical or nonsurgical shunts.

Surgical and Angiographic Shunts

When portal hypertensive bleeding (esophageal or gastric varices or portal hypertensive gastropathy) cannot be controlled with medical or endoscopic therapy, surgical and angiographic portosystemic shunts should be considered.

There are several surgical shunt options: portocaval, interposition mesocaval, and splenorenal shunts. An additional surgical option to control variceal hemorrhage is esophageal transection. Portocaval, mesocaval, and proximal splenorenal shunts decompress the portal blood flow in a nonselective fashion and increase the risk of postoperative hepatic decompensation and/or encephalopathy. Nonselective shunt surgery that requires dissection of the porta hepatis should not be per-

formed in liver transplant candidates because subsequent scar formation can make liver grafting technically difficult *(22)*. The distal splenorenal shunt is a selective shunt that aims to preserve hepatic blood flow while selectively decompressing esophageal varices. The distal splenorenal shunt is appropriate for patients who are not actively bleeding *(23)*.

The ideal patient for a surgical shunt has portal hypertensive bleeding but no other comorbidities and relatively preserved hepatic function. The Childs-Pugh A and early Childs-Pugh B cirrhotic patients are examples of patients who are most likely to benefit from a surgical shunt. In a case series of carefully selected patients, 4-year survival after surgical shunting was 81%. This survival percentage approximates the long-term survival of liver transplantation *(24)*.

Surgical shunts are not currently recommended in an emergency setting with actively bleeding patients. For unstable patients, the minimally invasive transjugular intrahepatic portosystemic shunt (TIPS) offers safety advantages.

The interventional radiologist gains access to the hepatic vein under fluoroscopic guidance, usually by puncturing the right internal jugular vein. A parenchymal tract is created between intrahepatic branches of the portal and hepatic venous systems. The tract is subsequently dilated prior to placement of the TIPS. A metallic mesh stent can be placed across the tract, creating a lower pressure sink that leads to effective decompression of the portal circulation.

TIPS has gained favor over the surgical shunts because it can be offered to patients with decompensated cirrhosis (Childs-Pugh Class C). Moreover, TIPS is viewed as a bridge to transplantation because it does not alter the vascular anatomy in patients who are candidates for liver transplantation. Authors at one center compared transplantation outcomes in a series of 20 patients, 7 of whom underwent TIPS prior to transplant. The other 13 had no shunt procedure. There was a trend toward better survival and lower transfusion requirement among TIPS recipients *(25)*. In a larger series of 200 patients who received TIPS, 30-day mortality was 26% with a median follow-up of 40 months; the overall rebleeding rate was 25.5% *(26)*. However, other studies have refuted any benefit from prophylactic TIPS before liver transplantation.

Complications of TIPS include acute thrombosis or stenosis of the shunt, migration of the shunt, or erosion of the shunt through the vessel wall with portal-arterial or biliary-vascular fistulae *(25)*. Encephalopathy is seen in up to 50% of patients post TIPS and usually responds to lactulose with or without neomycin in 90% of cases. The risk factors for

post-TIPS encephalopathy are pre-TIPS encephalopathy, female gender, nonalcoholic liver disease, decompensated liver disease, or the use of large-diameter stents. A recent study showed a five times higher incidence of encephalopathy in patients who had forward flow in their portal vein prior to the procedure rather than hepatofugal flow *(27)*.

Following placement of the intrahepatic shunt, serial Doppler ultrasound examination every 3 months is needed to assess for patency of the TIPS. In patients with recurrent variceal bleeding, a venogram of the TIPS must be performed to rule out thrombosis or stenosis. If necessary, the shunt can be revised at the time of angiography.

PREVENTION OF PORTAL HYPERTENSIVE BLEEDING

Prevention of the first and subsequent variceal hemorrhages requires a blend of pharmacologic and endoscopic therapies. Several studies have evaluated the efficacy of pharmacotherapy to decrease the risk of bleeding in patients with known portal hypertension. Pharmacologic efforts at prevention have focused on reducing portal hypertension by reducing portal blood flow, whereas endoscopic techniques strive to obliterate varices prophylactically.

Nonselective β-adrenergic antagonists such as nadolol or propanolol are widely regarded as the first step to prevent variceal hemorrhage. By blocking β_1 and β_2 receptors, drugs such as nadolol and propanolol reduce cardiac output (β_1) and block mesenteric vasodilation (β_2). The effect on β_2 receptors in the splanchnic bed allows unopposed vasoconstriction mediated by α-adrenergic receptors. Thus, both decreased inotropy and chronotropy by the heart and unopposed splanchnic vasoconstriction combine to decrease portal blood flow. The optimal dose of a nonselective β-blocker will lower hepatic venous pressure gradient by 20% *(5)*. When invasive measurements are not available, the target can be a reduction in the mean pulse by 25%. Metaanalyses of placebo-controlled trials have shown that β-blocker therapy significantly reduces bleeding risk in cirrhotic patients with portal hypertension and may improve mortality *(5)*.

Isosorbide mononitrate and other venodilators reduce portal hypertension by reducing intrahepatic vascular resistance, dilating portal-systemic collaterals, and generating a reflex splanchnic vasoconstriction, which decreases portal flow. A randomized, controlled trial has shown that nitrate therapy is as safe and effective as propanolol for prevention of a first variceal bleed *(28)*. Long-acting nitrates have also been studied in combination with β-blockers. A 50% reduction in the rate of hemorrhage has been reported *(29)*. However, because the addition of nitrates

can produce significant hypotension, these medicines may not be tolerated in patients with advanced cirrhosis.

Endoscopic sclerotherapy for prophylaxis of first variceal bleeding has not been shown to reduce morbidity or mortality, and its role is most likely limited to the acutely bleeding patient. Endoscopic variceal ligation, however, is widely endorsed for secondary prevention and is currently being studied for primary prevention of esophageal variceal hemorrhage. It may also be combined with nonselective β-blockers to prevent rebleeding in high-risk patients.

COMPLICATIONS AND OTHER ISSUES

Patients with portal hypertensive bleeding are at risk for several systemic complications. Respiratory complications such as aspiration pneumonia and respiratory failure can occur. Infections, worsening hepatic function, and renal failure from either acute tubular necrosis or hepatorenal syndrome are other possible sequelae.

In patients with cirrhosis, ascites, and portal hypertensive bleeding, there is a high incidence of spontaneous bacterial peritonitis. It is unclear whether one is pathophysiologically linked to the other, but infection of ascitic fluid and a systemic inflammatory response may cause significant morbidity even when acute bleeding has been controlled. The postulated mechanisms include enteric bacterial translocation and reduced complement activity and opsonizing activity in ascitic fluid. It is advised that all patients with ascites receive a diagnostic paracentesis for cell count with differential and culture and sensitivity. When a diagnostic tap is not possible, empiric antibiotic therapy with a third-generation cephalosporin, such as cefotaxime, is suggested until the patient's condition allows sampling of the peritoneal fluid.

CONCLUSIONS

Portal hypertensive bleeding is the most severe form of GI hemorrhage. Physicians must be keenly aware of the clinical signs of portal hypertension. A bleeding patient must be stabilized acutely with volume resuscitation, blood products, and vasoactive drugs. Prompt endoscopic evaluation can halt persistent bleeding, confirm a diagnosis, and risk-stratify the patient for recurrent hemorrhage. Prevention of recurrent bleeding depends on appropriate use of β-blocker therapy and endoscopic, surgical, or angiographic variceal decompression. In addition to stabilizing the patient and preventing rebleeding, the physician must be alert to systemic complications of the hemorrhage.

Approach to Patient with Active Portal Hypertensive Bleeding

1. Stabilization with intravenous fluids, reverse coagulopathy
2. Initiation of octreotide or vasopressin with nitrates
3. Endoscopic evaluation with possible sclerotherapy or banding
4. Serial endoscopic sessions until variceal obliteration *or* consideration for TIPS or surgical shunt *or* liver transplant
5. Secondary prophylaxis with nonselective β-blockers ± nitrates.

Approach to Patient with Portal Hypertension but no Prior History of Bleeding

1. Endoscopic evaluation to assess for presence of varices or portal hypertensive gastropathy in patients with cirrhosis
2. If varices are moderate or large, initiation of primary prophylaxis with nonselective β-blockers ± nitrates if tolerated
3. Consideration of hepatic venous pressure gradient measurement to ensure therapeutic efficacy of drug therapy or target a 25% reduction in baseline heart rate.

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7 Obscure Causes of Upper Gastrointestinal Bleeding

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CONTENTS

INTRODUCTION

Obscure bleeding is defined as bleeding of unknown origin that persists or recurs, i.e., recurrent or persistent iron deficiency anemia (IDA), fecal occult blood test (FOBT) positivity, or visible bleeding, after a negative initial or primary endoscopy (colonoscopy and/or upper endoscopy) result *(1)*. It has an estimated prevalence of approximately 5% in patients with upper gastrointestinal (GI) bleeding. Obscure bleeding can have two clinical forms: (a) *obscure-overt*, with recurrent passage of visible blood; and (b) *obscure-occult*, as manifested by recurrent IDA and/or recurrent positive FOBT results. This chapter discusses the various etiologies for obscure upper GI bleeding, with a focus on the diagnostic workup and management of these disorders.

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ETIOLOGY

The overall incidence and location of specific lesions responsible for obscure bleeding are unknown because there are no longitudinal studies addressing this issue. In protocols using enteroscopy in obscure bleeding, a source within reach of the standard upper endoscope was found at enteroscopy in 28–75% of patients whom a diagnosis was made *(2)*.

Upper GI lesions found in patients with obscure bleeding include peptic ulcer disease in 0–11%, erosions within large hiatal hernias (Cameron's erosions 0–8%), and gastric or duodenal vascular malformations in 0–8%. Less common upper tract sources of obscure bleeding are esophagitis, esophageal ulcer, esophageal varices, gastric or duodenal polyps, Dieulafoy's lesion, gastric antral vascular ectasia (GAVE; also known as watermelon stomach), blue rubber bleb nevus syndrome, Osler-Weber-Rendu syndrome, and celiac sprue (Table 1).

Cameron's Erosion

Cameron's erosions are linear erosions found in the body of the stomach, at or near the place where it was constricted by the diaphragmatic haitus *(3)*. In this area, the gastric mucosal folds often appeared swollen, erythematous, or with a mosaic-like surface. Erosions are frequently multiple and are usually seen on the crest of an inflamed-appearing fold. They are typically white, narrow, and elongated, with the longitudinal axis corresponding to the longitudinal direction of gastric mucosal folds. They usually present with IDA and rarely cause acute GI bleeding. Although treatment is most often supportive, surgical repair of the hernia can prevent recurrence of anemia by eliminating gastric mucosal trauma at the level of the diaphragm, allowing the linear erosions to heal.

A recent retrospective population analysis concluded that hiatal hernia should be included as a possible cause of iron deficiency anemia *(4)*.

GI Injury Induced by Nonsteroidal Antiinflammatory Drugs

See Chapter 5.

Gastric Antral Vascular Ectasia

GAVE is an increasingly recognized cause of occult bleeding. This condition is most common in elderly women. Patients generally experience occult bleeding and have IDA that fails to respond to oral iron therapy. Although the cause is unknown, it is seen at higher frequency with autoimmune or connective tissue disorders and atrophic gastritis, hypergastrinemia, cirrhosis, or portal hypertension. The typical endoscopic

Table 1
Causes of Obscure GI bleeding

Causes within reach of an upper endoscope
- Erosions within hiatal hernias (Cameron's erosions)
- Esophagitis (reflux, drugs, viral)
- Angiodysplasia
- Esophageal varices
- Peptic ulcer disease
- Gastritis
- Gastric polyps
- Gastric antral vascular ectasia
- Blue rubber bleb nevus syndrome
- Osler-Weber-Rendu syndrome
- Dieulafoy's lesion
- Celiac sprue
- Drug-induced injury (NSAIDs, biphosphonates, oral iron, and wax-matrix potassium chloride preparations)
- Duodenal tumors
- Duodenal varices
- Small bowel polyposis syndromes

Causes beyond reach of an upper endoscope
- Angiodysplasia
- Small bowel tumors (primary small bowel adenocarcinoma, metastatic lesions, lymphoma, leiomyoma, leiomyosarcoma, melanoma, carcinoid, and lipoma)
- Crohn's disease
- Celiac sprue
- Small bowel diverticulosis
- Small bowel varices
- Lymphangioma
- Radiation enteritis
- Ulcerative jejunoileitis
- Vasculitis (SLE, Henoch-Schönlein purpura, PAN, Behçet's disease, Churg-Strauss syndrome, cryoglobulinemia, giant cell arteritis, Köhlmeier-Degos syndrome)
- Blue rubber bleb nevus syndrome
- Osler-Weber-Rendu syndrome
- von Willebrand's disease
- Small bowel polyposis syndromes
- Neurofibromatosis
- Aortoenteric fistula
- Amyloidosis
- Meckel's diverticulum
- Hemosuccus pancreaticus
- Hemobilia
- Drug-induced ulcerations (NSAIDs, cocaine, and arterial chemotherapy)
- CMV-induced small bowel ulcers
- Small bowel ulcerations related secondary to infectious conditions (*Ascaris*, *Ancylostoma*, strongyloidosis, *Taenia saginata*, histoplasmosis, *Cryptococcus*, *Candida*)

Abbreviations: NSAID, nonsteroidal antiinflammatory drug; SLE, systemic lupus erythematosus; CMV, cytomegalovirus; PAN, polyarteristis nodosa.

appearance resembles stripes on a watermelon: rugal folds containing a column of vessels that converge at the pylorus. The optimal treatment has not yet been established. Supportive treatments with blood transfusions, steroid use, endoscopic ablation, or surgical treatments have all been reported *(5)*.

Dieulafoy's Lesion

Dieulafoy's lesion is a large artery very close to the mucosal surface, possibly as a congenital lesion. Traditionally, the name refers to a lesion in the proximal stomach, but up to one-third of Dieulafoy's lesions can be found elsewhere in the GI tract (most frequently the duodenum, but also in the esophagus, jejunum, and colon). The mechanisms that lead to bleeding have not been well characterized. Hemorrhage is caused by spontaneous thrombosis and perforation of an abnormally large (1–3 mm in diameter), tortuous, submucosal artery through the center of a solitary 2–5-mm gastric mucosal defect. Bleeding is frequently life-threatening. The usual presentation is with hematemesis, but hematochezia occurs in up to one-third of patients. Dieulafoy's lesion is found in 0.2–6.7% of patients with upper GI hemorrhage and 1–2% of patients undergoing surgery for upper GI bleeding. In 37% of patients, more than one endoscopic procedure will be required to establish the diagnosis.

Endoscopic treatment with various ablative methods is successful in more than 95% of patients *(6)*. If bleeding cannot be controlled endoscopically, then surgery is indicated. Successful identification of Dieulafoy's lesion often requires labeling with India ink by the endoscopist prior to surgery. Endosonography is useful in the detection of Dieulafoy's disease in patients with unexplained upper GI bleeding. Sclerotherapy can be performed during the same procedure, with endosonography-guided injection of the sclerosing agent near the abnormal vessel *(7)*.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome is characterized by blue-colored vascular nevi of the skin (but not mucous membranes). GI bleeding is also characteristic and is caused by the presence of cavernous hemangiomas, which can be located throughout the GI tract but are most common in the small bowel. Most cases are sporadic. Less commonly, autosomal dominant transmission has been reported. The GI lesions can be seen endoscopically and are best treated by endoscopic ablative methods *(18)*. Surgical resection is indicated for recurrent hemorrhage.

Osler-Weber-Rendu Syndrome

Osler-Weber-Rendu syndrome is also known as hereditary hemorrhagic telangiectasia. It is inherited in an autosomal dominant manner and is characterized by telangiectasias of the skin and mucous membranes and recurrent GI bleeding. Telangiectasias are most common in the stomach and small bowel, although they can be encountered in the colon as well. Bleeding is usually encountered as melena. Although the optimal treatment method has not been determined, lesions can be treated with endoscopic ablation. If endoscopic treatment fails, then surgical resection can be performed. Combination estrogen/progesterone hormonal therapy can reduce the transfusion requirements. Hormonal therapy is best used in patients with diffuse lesions or lesions that are inaccessible to endoscopic or surgical treatment *(9)*.

Hemobilia

Hemobilia is bleeding into the upper GI tract from the biliary tree. The most important causes include hepatic trauma, hepatic aneurysm, iatrogenic liver injury [e.g., liver biopsy, percutaneous transhepatic cholangiography, and transjugular intrahepatic portosystemic shunt (TIPS)], tumor erosion into the biliary tree, and gallstones. Diagnosis is suspected in patients who present with jaundice, right upper quadrant pain, upper GI hemorrhage, and laboratory evidence of cholesthasis. The initial evaluation of suspected hemobilia should include esophagoduodenoscopy (EGD), preferably with a side-viewing duodenoscope because blood is observed emanating from the papilla of Vater in 10–40% of cases. The precise cause is identified by angiography. Treatment depends on the specific cause of hemobilia and often involves embolization of the bleeding end vessel or surgery *(10)*.

Hemosuccus Pancreaticus

Hemosuccus pancreaticus results from erosion of a blood vessel into a pancreatic pseudocyst that communicates with the pancreatic duct. Although chronic pancreatitis causes an aneurysm of adjacent arteries in 10% of cases, only 1% of patients with chronic pancreatitis develop hemosuccus pancreaticus. Patients often present with shock followed by upper GI bleeding. Melena is more common than hematemesis. The diagnosis must be suspected when any patient with pancreatitis or a pseudocyst suddenly develops hypovolemic shock. The diagnosis is confirmed by noting frank bleeding from the ampulla. The source is identified by angiography, and treatment is either embolization of the bleeding vessel or surgery *(11)*.

Lesions in the Small Intestine

The small bowel is the least frequent site of obscure GI bleeding, being the source in only 3–5% of patients. The most common sources of obscure bleeding from the small intestine are vascular malformations, reported in 8–40% of patients *(12)*. Small bowel tumors are the second most frequent source of small bowel bleeding *(13)*. Among patients with occult bleeding who are evaluated by push enteroscopy, vascular malformations are present in 0–6% *(14)*. The findings with sonde enteroscopy report vascular malformations in 20–40% of patients and tumors in 0–8% *(15)*. Less common sources of small intestinal bleeding are Crohn's disease, small bowel varices, diverticula, ulcers, Meckel's diverticulum, ischemia, celiac sprue, aortoenteric fistula, radiation enteritis, ulcerative jejunoileitis, blue rubber bleb nevus syndrome, Osler-Weber-Rendu syndrome, Dieulafoy's lesion, polyposis syndromes, amyloidosis, hemosuccus pancreaticus, and hemobilia. Treatment modalities are directed toward the underlying etiology.

Vascular Malformations

Vascular malformations are also termed angiodysplasias and vascular ectasias and are responsible for 70–80% of small bowel bleeding.

A vascular malformation is a dilated complex of preexisting submucosal arterioles, capillaries, and venules that can usually be seen by endoscopy or angiography. True arteriovenous malformations, in contrast, are composed of thick-walled arteries and veins that are not connected by capillaries. Historically, vascular malformations that caused bleeding were thought to be located predominantly in the right colon. However, it is now

clear that vascular malformations can cause bleeding in any location: left colon, stomach, or small bowel. Multiple lesions are present in 30–75% of patients. Vascular malformations are probably best considered as a degenerative disease of aging, because they are most common in patients older than 60 years. The exact prevalence in the general population is unknown because many patients are asymptomatic, with lesions discovered only incidentally during bowel resection for another indication or during autopsy. Based on these data, their prevalence in the general population is estimated to be approximately 3% *(16)*. Aortic stenosis and chronic renal failure have been reported to be associated with vascular malformations, although a recent review of the literature shows no clear association between aortic stenosis and vascular malformations *(17)*. A recent study indicated that most patients with bleeding angiodysplasia or telangiectasia have a deficiency of the largest

multimers of von Willebrand factor induced by latent acquired von Willebrand's disease *(18)*. The natural history of vascular malformations is variable. Vascular malformations that are identified incidentally rarely bleed. Approximately 50% of patients with untreated or medically treated vascular malformations who have experienced a bleeding episode will have an additional bleeding episode that requires transfusion *(19)*.

Aortoenteric Fistulae

Although arterial fistulae into the esophagus and stomach have been reported, about 80% of aortoenteric fistulae communicate with the duodenum. Since the third portion of the duodenum is relatively fixed retroperitoneally between the abdominal aorta posteriorly and the mesenteric artery and vein anteriorly, it is subject to pressure necrosis from an infrarenal aneurysm (primary type) or from an aortic graft (secondary type). Most occur several years after initial graft placement, but cases have been reported as early as the immediate postoperative period.

The diagnosis of a secondary-type aortoduodenal fistula should be suspected when a bile-stained vascular prosthesis is recognized, a pulsatile mass is appreciated, or arterial bleeding is encountered in the second or third portion of the duodenum during endoscopy. Recognition of early symptoms of back pain, fever, and intermittent bleeding are helpful in alerting the physician to the possibility of impending aortoenteric hemorrhage. It is mandatory that endoscopy include examination of the third and fourth portions of the duodenum; otherwise, diagnosis of the aortoduodenal fistula will not be made. Some surgeons believe that upper GI endoscopy is needed only to exclude another cause of hemorrhage in a patient with known aortic prosthesis and that visualization of the fistula should not even be attempted. Computed tomography (CT) scan usually provides more valuable information than endoscopy and angiography. Preoperative imaging studies yield a diagnosis in fewer than 50% of cases.

Despite this low sensitivity, preoperative diagnosis should be attempted unless hemodynamic instability dictates immediate surgery. Fiberoptic endoscopy with visualization of the third portion of the duodenum, preferably with a pediatric colonoscope, should be the initial endoscopy study. Relatively obscure episodes of bleeding may occur initially, but massive exsanguinating hemorrhage eventually results. Many investigators stress the importance of visualizing the distal end of duodenum within the operating room in the event that a stable clot is dislodged and precipitates a massive bleeding. Significant upper GI

hemorrhage and the absence at endoscopy of other potential causes in a patient with an aortic graft is a distinct possibility in patients with this condition *(20)*. Two cases have been reported in which a graft constructed for a mesocaval shunt for control of esophageal variceal bleeding was seen protruding into the second portion of the duodenum at endoscopy *(21)*.

HISTORY AND PHYSICAL EXAMINATION

History and physical examination may sometimes provide clues to the cause of obscure GI bleeding. A directed history can reveal the use of medications known to cause mucosal damage or exacerbate bleeding [nonsteroidal antiinflammatory drugs (NSAIDs), alendronate, potassium chloride, and anticoagulants]. A family history of GI blood loss will expand the differential diagnosis to include hereditary hemorrhagic telangiectasia, blue rubber bleb nevus syndrome, and intestinal polyposis. Typical lesions can be found on the upper extremities, lips, and oral mucosa in patients with hereditary hemorrhagic telangiectasia. Patients with blue rubber bleb nevus syndrome can have cutaneous hemangiomas in addition to those in the GI tract. Some rare causes with typical findings on physical examination include celiac sprue (dermatitis herpetiformis), AIDS (Kaposi's sarcoma), Plummer-Vinson syndrome (brittle, spoon-shaped nails, atrophic tongue), pseudoxanthoma elasticum (chicken-skin appearance, angioid streaks in the retina), Ehlers-Danlos syndrome (hyperextensible joints, ocular and dental abnormalities), neurofibromatosis (café-au-lait macules, axillary freckles, cutaneous neurofibromas), and malignant atrophic papulosis (discrete painless papules). Certain polyposis syndromes (e.g., Peutz-Jeghers syndrome, Gardner's syndrome, Cronkhite-Canada syndrome, Cowden's disease) can also have typical cutaneous manifestations, as can neoplastic disease (Sister Mary Joseph nodule of the umbilicus and left supraclavicular enlargement in intraabdominal malignancy, tylosis in esophageal cancer).

EVALUATION

Upper or lower intestinal site-specific symptoms may direct the initial endoscopic procedure, but conflicting data do not support limiting the evaluation to the symptomatic region. When a source for blood loss is not apparent from the examination of colon and the upper GI tract, the small bowel is usually interrogated. Before examination of the small intestine, repeat upper endoscopy and colonoscopy can also be helpful to identify lesions that are overlooked at initial endoscopy (Fig. 1).

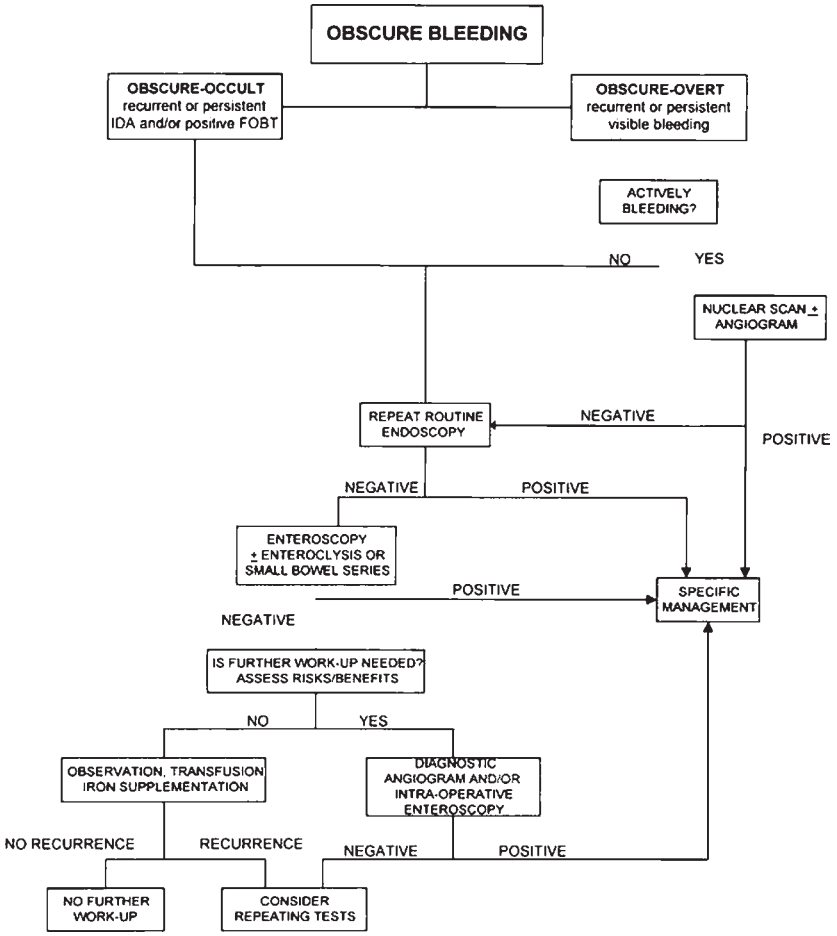

Fig. 1. Algorithm for evaluation of obscure bleeding. FOBT, fecal occult blood test; IDA, iron deficiency anemia (from ref. *1*, with permission).

In one study of 17 patients with obscure blood loss, 35% had a bleeding source identified on repeat endoscopy (upper endoscopy 29%, colonoscopy 6%) *(22)*. Even when the intent is to examine the small bowel with an enteroscope, a source that should have been discovered at the prior endoscopy was found in 28–75% of patients in whom a diagnosis was made by enteroscopy *(23)*. The most common lesions missed during upper endoscopy include erosions within large hiatal hernias (Cameron's erosions), peptic ulcer disease, and vascular ectasia. However, one report of 39 patients with obscure bleeding found no additional diagnostic yield when upper endoscopy and colonoscopy were repeated.

DIAGNOSTIC TECHNIQUES

Small Bowel Biopsy

Small bowel biopsy performed during upper endoscopy or enteroscopy may be used to detect celiac sprue as a cause of IDA *(24)*. Although as many as one-half of anemic patients with untreated celiac disease have iron deficiency, the prevalence in IDA is much lower, 0–11%. This finding may be related to various factors, including age, disease prevalence in the country of origin, and referral bias. Small bowel biopsies performed during upper endoscopy, as a part of a protocol evaluating 79 patients with IDA, did not find any causes of celiac sprue, whereas another protocol found histology-compatible sprue in 5.7% of 70 patients *(25)*.

The appearance of the small bowel during endoscopy may be a tip-off to the presence of sprue and the need for biopsy. Gross findings include loss or effacement of circular folds or rings of Kerckring, scalloping of the circular folds, and smooth atrophic-appearing mucosa with pallor and a pronounced vascular pattern. Another simple screening technique relies on the increased magnification created by viewing the small bowel mucosa while the tip is submerged under water and then observing for the presence or absence of villi.

Demographic and clinical features may also help assess the need for a small bowel biopsy. Celiac disease is rare if not nonexistent among African-Americans and Asians. Lack of response to oral iron therapy may also be a clue to the possibility of sprue. A confounding issue in the evaluation of occult and obscure bleeding is the recent evidence of positive FOBT results in approximately half of patients with celiac sprue *(26)*.

Peroral and Transnasal Enteroscopy

Endoscopic examination of the small bowel has evolved around two main techniques: push enteroscopy, involving peroral insertion of long endoscope directly into the jejunum, and sonde enteroscopy, in which the enteroscope is usually inserted transnasally and the tip is propelled by peristalsis.

Push enteroscopy has since evolved into the standard approach for further evaluation of obscure bleeding, facilitated by the availability of long videoscopes and relative ease of use *(27)*. Fluoroscopy has been used to assess depth of insertion of the enteroscope, but it is not routinely used; plain abdominal radiographs have also been used to document the point of deepest insertion. An overtube can be used to assist deep intubation and to avoid looping in the stomach, although some investigators report no clear advantage and complications with its use. The depth of

insertion past the ligament of Treitz can range from 15 to 160 cm. One study reported mean lengths of insertion past the ligament of Treitz of 108 cm with an overtube (range, 60–150 cm) and 11 cm without an overtube (range, 5–30 cm) *(28)*. Studies addressing the yield of push enteroscopy in the investigation of obscure-overt and obscure-occult bleeding were similar in one study *(29)* (72 and 69%, respectively) but differed some what in another (37 and 55%, respectively). Push enteroscopy appears to be a relatively safe procedure, with a low incidence of complications, some of which are related to the overtube. Complications reported include postprocedure abdominal pain, acute pancreatitis, Mallory-Weiss tear with bleeding requiring cauterization, and a pharyngoesophageal tear.

Sonde enteroscopy was developed in the late 1970s and provides the potentials for direct examination of the entire small bowel mucosa. After transnasal or oral passage into the stomach , the tip is dragged into the proximal small bowel with the aid of an endoscope. Intrinsic gut peristalsis can propel the balloon at the tip of the endoscope into the terminal ileum. Inspection is carried out on withdrawal of the enteroscope. Sonde-type enteroscopy is less popular than push-type enteroscopy. Patient discomfort is aggravated by the length of the procedure (average insertion time, 4 hours; average withdrawal/examination time, 45 minutes). Mucosal visualization is limited because of lack of four-way tip deflection and relatively uncontrolled instrument withdrawal. Moreover, an alternate mode of intervention is necessary for therapy. The advantage of sonde enteroscopy is the potential for total small bowel examination, with ileal intubation rates reported at 60–75%. The double-balloon method has recently been reported to facilitate endoscopic access to the small intestine.

Complications are said to be uncommon, although bowel perforation occurred in 3% of patients in one series. In another series, 14% of patients developed epistaxis, and epistaxis requiring nasal packing has also been reported. The overall diagnostic rates range from 26 to 54%. The yield was highest when closed biopsy forceps passed through the instrument channel and were used to push away the bowel wall, thereby allowing better mucosal visualization *(30)*. In one study that combined push-type and sonde-type enteroscopy in the same patients, 18% had lesions within push-type enteroscopy limits, whereas 26% had bleeding sources beyond the limits of push-type enteroscopy; 40% had lesions that were within the limits of the upper endoscope *(31)*. Newer sonde-type enteroscopes have been developed with videoptics, a wider field of vision, and two-way tip deflection. It remains to be seen whether these improvements increase the popularity of sonde enteroscopy.

Retrograde Enteroscopy

Retrograde enteroscopy involves examination of the distal ileum at colonoscopy using a standard colonoscope, a small bowel enteroscope, or a smaller endoscope passed through the instrument channel of a specially designed therapeutic colonoscope. The ileocecal valve is intubated 72–79% of the time at routine colonoscopy, the length of terminal ileum examined is variable, and the diagnostic yield has been reported to be up to 2.7%. In a study in which push enteroscopy from above was combined with retrograde ileoscopy (using a small bowel enteroscope) in the investigation of obscure GI bleeding and IDA, ileoscopy provided a diagnosis in 1.3% of cases; the mean length of the ileum examined was 60 cm (range, 20–120 cm). In the only report on the use of a second 3.4-mm-diameter endoscope passed through the instrument channel of a colonoscope, the procedure was complicated by technical problems, and adequate visualization was achieved in only 70%; abnormalities were seen in 20%. However, dedicated retrograde enteroscopy appears to have a low yield and should be reserved for instances in which other evidence indicates a potential source of blood loss in the terminal ileum *(32)*.

Intraoperative Enteroscopy

Intraoperative enteroscopy (IOE) is usually applied in cases of transfusion-dependent bleeding that is not localized in spite of extensive diagnostic evaluation, with or without preceding nonoperative enteroscopy. In these instances, the severity of the blood loss warrants further workup, and the risks of continued bleeding outweigh the risks of laparotomy. Laparotomy has been coupled with the passage of an endoscope orally, transnasally (using a sonde endoscope), *per rectum*, or through enterotomies performed on the small bowel. When it is performed for obscure GI bleeding, the ability of IOE to identify potential bleeding lesions has been impressive, ranging from 70 to 100% *(33)*. However, finding a lesion does not always equate cessation of bleeding.

Technical difficulties with scope advancement have been attributed to dense adhesions or infiltrating neoplasia. Obscured visibility caused by luminal blood has been a problem that may be improved with oral purging. Complications range from 0 to 52% and include mucosal laceration, intramural hematomas, mesenteric hemorrhage, perforation, prolonged ileus Ogilvie's syndrome, intestinal ischemia, intestinal obstruction, stress ulcer, wound infection, and postoperative pulmonary infection. Mortality related to the procedure or postoperative complica-

tions has been up to 11%; however, most studies reviewed do not report mortality with IOE *(34)*.

IOE has also been performed through single or multiple intestinal incisions. The advantages of IOE through an enterotomy include elimination of intestinal dead space (i.e., esophagus, stomach, and duodenum, or colon and rectum) that presumably was already extensively examined before IOE, and decreased trauma to the bowel. Comparative data for morbidity and mortality of nonenterotomy and enterotomy are not available, although it has been suggested that the addition of enterotomy to laparotomy does not increase morbidity or mortality. However, this method could miss lesions in the parts of the bowel that are bypassed, as suggested by reports that 22% of patients undergoing IOE without enterotomy had a bleeding source proximal to the duodenum, and 13% had a source distal to the ileocecal valve *(35)*. A combined laparoscopic and endoscopic approach to GI bleeding has also been performed for evaluation of obscure GI bleeding, but many technical questions remain.

The use of a sonde enteroscope during laparotomy reportedly facilitates intestinal passage because of its small radius of curvature, which reduces mucosal artifacts. However, the field of vision of a standard sonde enteroscope is less than that of a standard enteroscope or a colonoscope. Newer video sonde enteroscopes with a wider field of vision and tip deflection may eliminate some of the problems associated with the older enteroscopes.

The choice of the instrument type and entry site will necessarily depend on the instrument availability, familiarity with the diagnostic approaches, and the experience and technical expertise of both the surgeon and the endoscopist. Because of the initial capital expense of purchasing a dedicated enteroscope and the relative low prevalence of obscure bleeding cases, standard and pediatric colonoscopes will probably continue to be used as enteroscopes.

Capsule Endoscopy

A promising technology that has been recently introduced to clinical practice in gastroenterology is capsule endoscopy. Wireless capsule endoscopy has recently been shown to be superior to push enteroscopy in an animal model *(36)*. The first case series of obscure bleeding provided good views from the mouth to the colon and successfully imaged small bowel pathologic features *(37)*. Although this technology cannot be used for biopsy or therapy, it may prove valuable in the assessment of bleeding with negative results on gastroscopy and colonoscopy. Clinical trials to assess the efficacy of capsule endoscopy will be interesting.

Small Bowel X-Ray Series and Enteroclysis

Barium studies are often used for further workup of the small bowel in obscure bleeding, either before enteroscopy or when push enteroscopy has failed to reveal a source. *Per oral* ingestion of a barium suspension is used for the small bowel follow-through (SBFT) X-ray series, whereas enteroclysis involves instillation of contrast material through a small tube placed in the proximal intestine either directly or facilitated by endoscopy. Diluted methylcellulose solution enhances the double contrast effect, thereby improving the quality of the study. Although radiation exposure and patient discomfort are higher with enteroclysis, studies have documented significantly higher overall diagnostic yield, higher sensitivity, and shorter procedure times than with SBFT. When enteroclysis is used for the diagnosis of obscure bleeding, its yield can range from 10 to 21%, which is higher than the yield of SBFT (0–5.6%). The sensitivity of enteroclysis in the diagnosis of small bowel neoplasia is much higher, approaching 95% *(38)*. Although enteroclysis has been suggested as the radiologic study of choice for the investigation of suspected gross disorders of the small bowel, there is a low yield in the diagnosis of angiodysplasia. In one report of 128 enteroclysis studies performed for obscure bleeding, only 2% had subtle findings suggestive of angiodysplasia and substantiated on pathologic examination of resected bowel.

Enteroclysis may be complementary to enteroscopy when performed after a negative examination result *(39)*. Because nasal placement and pyloric intubation are the most uncomfortable aspects of enteroclysis tube placement, recent diagnostic endeavors have used endoscopic placement of the enteroclysis tube after a negative push-type enteroscopic examination. The insufflation of air during enteroscopy and the administration of conscious sedation and glucagon do not seem to compromise the quality of radiographs. Enteroscopy applied in this piggyback technique was helpful in making a positive diagnosis in 8% of patients with negative enteroscopy results and improved the yield of enteroscopy from 54 to 57%.

Magnetic resonance (MR) enteroclysis has recently been introduced as a diagnostic modality for evaluation of the small bowel. To be the primary method for investigation of small bowel disease, MR enteroclysis will have to provide reliable evidence of normalcy, allow diagnosis of early or subtle structural abnormalities, influence treatment decisions in patient care, and be cost-effective; none of these issues has been clarified so far *(40)*.

Nuclear Scans

The in vitro technetium 99m-labeled red blood cell (TRBC) scan is the most used method of radioisotope scanning, its advantage being the long half-life of the label, which allows for repeat scanning if necessary over a 24-hour period. The TRBC scan requires a bleeding rate of 0.1–0.4 mL/min for a positive result and is readily available and safe *(41)*.

Specific data on the utility of TRBC scans in obscure GI bleeding are limited. In a preliminary report, 24% of all positive TRBC scans performed for presumed acute lower GI bleeding were localized to the small bowel.

Meckel's scanning using TC-99m-pertechnate is also used for the evaluation of small bowel bleeding. The sensitivity is reported to be 75–100%. Enhanced scans are performed using pentagastrin or cimetidine to increase the uptake of pertechnate, which can increase the sensitivity of the scan. However, a positive scan result only indicates the presence of gastric mucosa, which may or may not represent the bleeding source.

Intraoperative scintigraphy has been advocated as a worthwhile method for intraoperative localization of bleeding segment. The bowel segment is clamped every 30 cm, and a γ-camera assesses the presence of labeled blood within the clamped segment. Other investigators have successfully used a hand-held Geiger counter in similar circumstances, but the procedure is cumbersome and time-consuming.

Angiography

The role of angiography in obscure bleeding is difficult to assess because a limited number of angiographic protocols specifically address obscure bleeding. When active bleeding occurs at a rate of greater than 0.5 mL/min, extravasation of contrast into the bowel lumen may be found on mesenteric angiography *(42)*. Administration of anticoagulants, vasodilators, or clot-lysing agents can potentially propagate or precipitate bleeding and improve the yield of angiography. The potential risk of uncontrolled bleeding limits the use of this technique to selected cases that are without significant comorbid illnesses in whom other modes of diagnosis have been exhausted *(43)*.

Angiography has also been performed intraoperatively to assist the surgeon in localizing a bleeding lesion. Superselective catheter placement and methylene blue injection during laparotomy have helped localize small bowel angiodysplasia and bleeding mucosal erosions so that segmental bowel resection of the stained bowel segment can be performed. Other investigators have also used superselective preoperative or intraoperative methylene blue, fluorescein, or radiopaque coil

injection into the bleeding artery to localize the lesions for resection. The indications and utility of each of these angiographic techniques need further evaluation.

Exploratory Laparotomy

Currently, exploratory laparotomy for obscure bleeding is seldom reported without concomitant IOE. In one series from the 1980s, 64% of 14 patients who underwent exploratory laparotomy without IOE had a diagnosis made at surgery. In another series, 24 (65%) of 37 patients undergoing surgery for obscure bleeding had a lesion identified by simple palpation and transillumination alone.

Other Techniques

The use of meperidine for conscious sedation during endoscopy may reduce mucosal blood flow and mask the detection of angiodysplasias. Consequently, the use of narcotic antagonists like naloxone or the avoidance of meperidine may enhance the appearance of GI angiodysplasias *(44)*. Biphasic arterial- and venous-phase CT scanning has been used for identification of angiodysplasia. The bowel is distended by water, and intravenous contrast is rapidly injected using a power injector. Arterial- and venous-phase helical CT scans are obtained sequentially after an unenhanced scan. Angiodysplasias were noted during the arterial phase, and additional lesions became visible during the venous phase of the study *(45)*. Doppler ultrasonography has been reported to detect increased blood flow through angiodysplasia and has been used intraoperatively with a hand-held probe to confirm lesions initially identified by transillumination.

MANAGEMENT

Although the management of the primary disorder leading to occult or obscure bleeding can vary depending on the nature of the disorder, management of blood loss generally falls into the following categories: endoscopic therapy, angiographic therapy, pharmacotherapy, surgery, and nonspecific measures (Fig. 1).

Endoscopic Therapy

Angiodysplasias, gastric antral vascular ectasia, vascular malformations in blue rubber bleb nevus syndrome, and hereditary hemorrhagic telangiectasia have been treated successfully using thermal contact probes, injection sclerotherapy, argon plasma coagulation, and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.

However, most angiodysplasias are not bleeding at the time of the diagnosis, and up to 50% of patients with angiodysplasia found upon investigation of GI bleeding do not have bleeding again over several years of follow-up. Nonbleeding angiodysplasia is also found with other potential sources of bleeding. Endoscopic cauterization of bleeding angiodysplasia found on enteroscopy has been shown to decrease the requirement of blood transfusions significantly compared with no treatment *(46)*. In a trial using the Nd:YAG laser, sustained reduction of transfusion requirements was found in 100% of patients with angiodysplasia, 75% with gastric vascular ectasia, and 66% with hereditary hemorrhagic telangiectasia *(47)*. Other studies have reported bleeding rates of 13–26% over 1 year of follow-up with the use of the Nd:YAG laser for angiodysplasia ablation. Slightly higher bleeding rates (up to 34%) have been reported with the use of thermal contact devices.

Angiotherapy

The number of patients successfully treated with vasopressin infusion or embolization for obscure-overt small bowel bleeding is limited and is reported as a part of larger series involving transcatheter treatment of small bowel and colonic sources of acute bleeding. Methylene blue dye injection into the bleeding artery at angiography stains the mucosa of the small bowel and can be helpful in directing the surgeon to the appropriate bleeding segment.

Angiotherapy is not without complications that are sometimes serious and life-threatening. Major cardiovascular complications have been noted in 9–21% of patients receiving intraarterial vasopressin, including myocardial infarction, arrhythmias, hypertension, and thrombosis of arteries remote from the bleeding site. Complications with embolization were noted in 17% of patients in one series, including ileus, intestinal infarction requiring surgical resection, fistulization between bowel segments, and arterial thrombosis. Ischemic complications have been reported less often when embolization is performed for small bowel or gastroduodenal bleeding rather than colonic bleeding. Embolization may have utility in patients with coronary artery disease or other disorders in which vasopressin infusion is relatively contraindicated or as an alternative to surgery in patients with significant comorbid conditions *(48)*.

Pharmacotherapy

Medical therapy for vascular lesions causing obscure GI bleeding is usually reserved for diffuse disease, for lesions in areas inaccessible to endoscopic therapy, when there is continued bleeding despite endo-

scopic therapy or surgical resection or when bleeding is recurrent, the diagnosis is unknown, and vascular lesions are suspected *(49)*. In uncontrolled open-label studies, patients with chronic renal failure and GI bleeding caused by angiodysplasia are reported to benefit from estrogen-progesterone combination therapy. In a double-blind randomized, crossover trial, six of eight patients with hereditary hemorrhagic telangiectasia and von Willebrand's disease stopped bleeding during the hormonal therapy arm. However, in a cohort study of patients with small bowel angiodysplasia, treatment with combination hormonal therapy did not alter transfusion requirements or rebleeding rates compared with untreated controls.

More recently, in a group of patients with persistent or recurrent obscure bleeding despite comprehensive endoscopic investigation, treatment with combination hormonal therapy stopped rebleeding in all patients as long as therapy was continued, a benefit not demonstrated with estrogen therapy alone. Although low estrogen combination therapy (ethinyl estradiol, 0.035 mg, in combination with norethisterone, 1 mg) has been reported to be effective, a higher estrogen combination (containing 0.05 mg ethinyl estradiol) may be required in subjects who do not respond to the lower dose combination. Some investigators recommend 6-month courses of therapy with treatment pauses to reduce the incidence of adverse effects. Reported adverse effects include breast tenderness and vaginal bleeding in women and gynecomastia and loss of libido in men. In one series, up to 57% of patients reported adverse effects; these effects necessitated cessation of therapy in 40%. Although the potential risk of thromboembolic events exists, one study found no difference in mortality from cardiovascular diseases between treatment and control groups.

Octreotide, in a dose of 0.05–0.1 mg subcutaneously two to three times a day, has been reported to reduce blood loss from intestinal angiodysplasia. Response is fast, with the disappearance of overt bleeding and improvement in transfusion requirements as early as 24 hours after initiation of therapy. In one instance, bleeding recurred when therapy was discontinued after 6 months. No significant adverse effects other than mild hyperglycemia were noted.

Other pharmacotherapeutic agents that have been used with partial success in epistaxis and GI bleeding from hereditary hemorrhagic telangiectasia include danazol (antigonadotrophin with weak androgenic activity) and desmopressin. Anecdotal reports suggest improvement in transfusion requirements with danazol but not with desmopressin in patients with diffuse angiodysplasia unresponsive to combination hormone therapy. Aminocaproic acid, an inhibitor of the fibrinolytic sys-

tem, was reported to be effective in two patients with hereditary hemorrhagic telangiectasia and epistaxis, although it is not certain whether these patients had concomitant GI bleeding.

Surgery

Most bleeding tumors will warrant surgical excision, and most other causes of obscure bleeding have the potential to require surgery if nonsurgical measures are ineffective for control of bleeding. Surgical exploration and subsequent bowel resection may also be necessary when bleeding is associated with high transfusion requirements. When patients present with exsanguinating GI bleeding, emergency surgery may be lifesaving. Simple bowel palpation and transillumination have traditionally enabled surgeons to identify culprit lesions requiring resection in up to 65% of patients undergoing exploratory surgery for obscure bleeding *(50)*. Intraoperative enteroscopy has added a new dimension to the surgical localization of obscure GI blood loss, and small bowel resections are generally associated with preoperative or concomitant localization of the bleeding source. In one series of 30 patients undergoing IOE, the findings directed surgical resection in all but 2 patients; other studies have reported similar good results. However, even surgical resection can be associated with rebleeding in up to 30% of patients. The lowest rebleeding rates after segmental bowel resection for bleeding angiodysplasia have been reported when angiographic localization of the bleeding source assisted resection.

Nonspecific Measures

Nonspecific measures in the management of occult and obscure bleeding include iron supplementation, correction of coagulation and platelet abnormalities, and intermittent blood transfusions if the anemia cannot be controlled with iron supplementation alone. Little information is available on how often nonspecific measures are required and their efficacy. When patients with bleeding GI angiodysplasia were treated with observation alone or intermittent transfusions, 54% had no rebleeding episodes during a 3-year follow-up period, suggesting that nonspecific measures are sufficient in some instances. These measures are beneficial when the rate of blood loss is slow and in elderly patients in whom the risk of further diagnostic evaluation is greater than the risk of nonspecific management.

Outcomes

Obscure bleeding has outcome measures that are uniquely different from those for acute and occult bleeding. The time from disease onset

to diagnosis may be much longer, adding to the costs incurred in making the diagnosis. In one study, the median time to diagnosis of obscure-overt bleeding was 2 years, with a range of 1 month to 8 years. More than 50% of patients with obscure bleeding have had at least two bleeding episodes before presentation for enteroscopy. When enteroscopy is performed after a previous negative upper endoscopy result, 28–75% of patients have lesions within reach of an upper endoscope diagnosed. Using Medicare reimbursement figures from 1997, an estimated cost savings of $187 per patient is anticipated if repeat upper endoscopy is replaced by enteroscopy *(51)*. One study of patients with obscure bleeding that required IOE noted a mean of 5 hospital admissions (range, 2–20) and a mean of 46 U of blood transfused (range, 6–200) before surgical intervention. No longitudinal studies have addressed the relative costs of diagnostic evaluation of obscure bleeding compared with occult or acute bleeding.

Enteroscopy with endoscopic ablation of angiodysplasia has been reported to improve hemoglobin levels significantly over long-term follow-up of patients with obscure bleeding. Significant decreases in transfusion requirements (13–6 U before lesion ablation vs. 6–3 U in the year after ablation; $p = 0.02$) have also been reported by other investigators. This has been associated with improvement in quality of life, as measured by a standard questionnaire. Pharmacotherapy with combination hormone therapy has also improved outcomes in selected patients with severe undiagnosed obscure bleeding, regardless of whether or not angiodysplasia has been found or endoscopically ablated. Other studies suggest that rebleeding rates are not much different whether endoscopic ablation, pharmacologic treatment, or no therapeutic intervention is pursued.

The outcomes of surgery for obscure bleeding are variable and probably depend on whether a bleeding source is discovered and resected at exploratory laparotomy. Intraoperative enteroscopy is reported to influence the type of surgery performed in more than 70% of patients, but over a 2-year follow-up, 20–52% of patients can develop rebleeding that necessitates transfusions. The long-term success rate of IOE-directed therapy in eliminating recurrent GI blood loss has ranged from 41 to 71%.

There appears to be no single efficient diagnostic approach or therapeutic panacea in the management of obscure bleeding. Most patients will benefit from a meticulous investigation routine that attempts to visualize as much of the bowel as necessary. For some, this will include multiple diagnostic procedures and eventually exploratory laparotomy. In other cases, the risks of further diagnostic procedures may be higher than the risks of nonspecific therapy with iron supplementation and

intermittent blood transfusions. Further outcome studies are needed to determine the most expedient diagnostic approach and optimal management strategies.

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8 Surgical Approach to Acute Upper Gastrointestinal Bleeding

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CONTENTS

INTRODUCTION

Acute upper gastrointestinal (GI) hemorrhage remains a common and significant problem throughout the world. The mortality rate for all patients approaches 10% and health care systems incur significant costs for the diagnosis and treatment of the disorders that cause this problem. Acute upper GI bleeding is defined as the loss of blood from any point in the GI tract proximal to the ligament of Treitz (esophagus, stomach, and duodenum) and accounts for approximately 80% of the cases of hemorrhage from the entire GI tract. Traditionally, surgery provided the only means to control ongoing GI bleeding. However, with the development of therapeutic endoscopy in the 1980s, less invasive management options are increasingly available. Despite the changes in the management of upper GI bleeding, the goals of treatment remain rapid and effective resuscitation of the patient, definitive control of ongoing

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hemorrhage, treatment of the underlying pathology, and prevention of recurrent bleeding. Today, effective management of this clinical problem requires an in-depth knowledge of a variety of common and uncommon disease processes that may be complicated by upper GI bleeding and the multidisciplinary treatment options currently at our disposal.

Hemorrhage, as a complication of peptic ulcer disease, decreased greatly after the introduction of histamine receptor antagonists and gastric acid proton pump inhibitors and the recognition of the role *Helicobacter pylori* plays in the pathogenesis of gastric and duodenal ulcers. However, although there is a relative paucity of recent studies documenting the epidemiology of upper GI bleeding, it remains a common problem. Data suggest that there are approximately 300,000 hospital admissions per year in the United States for upper GI bleeding, and, in both the United States and Europe, there is an incidence of 45–100 hospitalizations per 100,000 population *(1–3)*. Upper GI bleeding is more common in men than women, with a case ratio of about 3:2 men to women. Its incidence also strongly correlates with increasing age, being 20–30-fold higher in 80-year-old patients, compared with patients in the second decade of life. In addition, upper GI bleeding is more lethal in elderly patients. In data from the United Kingdom, mortality rises from 3% in patients younger than 60 years to 20% in patients older than 80 years *(3)*.

A crucial step in management of GI hemorrhage is to localize the bleeding source to the upper or lower GI tract. Hematemesis, either red blood or coffee-ground material, is the classic symptom/finding of upper GI bleeding. Hematemesis usually indicates a bleeding source proximal to the ligament of Treitz, and rare exceptions are in the very proximal jejunum. In the absence of hematemesis, a nasogastric tube should be placed into the stomach and the contents aspirated. Aspirated blood or coffee ground material has the same significance as hematemesis; aspiration of gastric juice containing bile is reassuring but does not absolutely exclude an upper GI source *(4)*. The passage of black, tarry, so-called melena usually results from the presence of blood in the proximal GI tract. Melena strongly suggests an upper GI source. Other symptoms or signs that are associated with upper GI bleeding include orthostasis, syncope, tachycardia, oliguria, and hypotension. These findings are helpful in determining the amount of bleeding that has occurred, but it should be remembered that an individual can lose a unit of blood (the amount that is safely donated) or more without significant signs or symptoms. Laboratory findings may document anemia, thrombocytopenia, coagulation disorders, fluid and electrolyte imbalances, and an elevated blood urea nitrogen/creatinine ratio.

Table 1
Major Causes of Upper Gastrointestinal Hemorrhage

Diagnosis	*Proportion of cases (%)*[a]
Peptic ulcer disease	34–52
Mucosal erosive disease	15–24
Esophagitis	
Gastritis	
Duodenitis	
Gastroesophageal varices	4–20
Mallory-Weiss tear	5
Dieulafoy's lesions	1
Neoplasms	2–4
Angiodysplasia	1
Hemobilia	<1
Aortoduodenal fistula	<1
Unknown	8–25

[a]The relative frequency of each of the diseases in three population-based series *(1–3)*.

Adequate resuscitation of the patient is essential for excellent outcome. It should begin before but may continue during efforts to localize the source of bleeding. Patients should not undergo procedures requiring sedation or intravenous contrast if they are hypovolemic or unstable. Adequate intravenous access with at least two large-bore catheters is mandatory. Crystalloid solutions and/or blood infusion are critical to restore circulating blood volume and to maintain oxygen delivery to tissues. Adequate amounts of blood and blood components must be readily available for use if bleeding continues or recurs. A urinary catheter should be placed early since it provides critical information about the adequacy of the patient's volume resuscitation. Elderly patients, patients with significant comorbidities, and unstable patients may require more invasive monitoring of intravascular volume, i.e., central venous monitoring or a pulmonary artery catheter.

After resuscitation, the next step in management is usually upper GI endoscopy. Ongoing bleeding may require immediate examination, but stable patients can be examined less urgently. Flexible upper endoscopy performed within 12 hours of presentation diagnoses the location and source of bleeding in more than 90% of cases and may be therapeutic if there is ongoing hemorrhage *(5)*. The wide variety of disorders that cause upper GI bleeding and the proportion of patients who present with these problems are listed in Table 1. Based on the diagnosis and findings

at endoscopy, an initial endoscopic attempt to control the source of hemorrhage may be attempted. In some patients, a second attempt at endoscopic management may be prudent, but ongoing hemorrhage after infusion of 4–6 U of blood more likely will need operative intervention. A detailed management and surgical approach is discussed below according to the disease process.

PEPTIC ULCER DISEASE

Peptic ulcer disease remains the most common cause of upper GI bleeding in most series, accounting for 35–50% of all cases if both gastric and duodenal ulcers are considered. Over the last 20 years, a number of advances in our understanding of the pathogenesis of peptic ulcer disease have altered the treatment and changed the role of surgery in this disease. With the elucidation of the role of *H. pylori* in ulcer pathogenesis and the advent of histamine antagonists, proton pump inhibitors, and therapeutic upper GI endoscopy, surgery for peptic ulcer disease has become much less commonplace. However, up to 15% of cases *(6)* are refractory to medical treatment and require surgical intervention. Indeed, patients requiring surgery today have problems that are more complex and associated with comorbidities and thus are more challenging for the surgeon.

The indications for operative intervention for bleeding peptic ulcers remain the same as in the past: (a) exsanguinating hemorrhage; (b) active bleeding that has failed medical and endoscopic therapy; (c) recurrent bleeding after effective medical therapy, especially if this occurs during the same hospitalization; and (d) treatment of other complications in addition to bleeding such as perforation obstruction or malignancy. A general rule of thumb is that any patient who requires 4–6 U of blood transfusion should be considered for surgical intervention. This guideline is, of course, modified according to the rate of hemorrhage and the condition of the patient. A common mistake is to make extraordinary attempts to avoid surgery by continuing blood transfusion and nonoperative interventions in a seriously ill or elderly patient. In fact, the morbidity and mortality increase with increasing transfusion. The best treatment in such patients may be definitive control of hemorrhage.

After resuscitation, upper endoscopy is the initial step in the management of the patient with bleeding peptic ulcer. If active bleeding cannot be controlled by endoscopic therapy, the patient needs an urgent operation. For this reason, a surgeon should be contacted who should become familiar with the patient, and the patient should be prepared for surgery before upper endoscopy is undertaken. The diagnosis of a gastric or

duodenal ulcer is usually straightforward, and characteristics of the ulcers important for prognosis and treatment, such as a visible vessel or evidence of malignancy, may be obtained. No evidence of active bleeding or control of bleeding at endoscopy stratifies the patient to a low risk for rebleeding and operative therapy.

Endoscopy allows intervention to control hemorrhage in up to 80–85% of cases. Endoscopic therapy of nonvariceal upper GI bleeding, using either injection therapy or thermal therapy, has been shown by metaanalysis to reduce significantly the risk of further bleeding and the need for emergency surgery if the patient exhibits active bleeding or a visible vessel *(7)*. Moreover, a recent randomized prospective trial by Lau et al. *(8)* comparing repeat endoscopy with surgery demonstrated that 75% of the patients achieve long-term control of bleeding with repeat endoscopy. This study also demonstrated that treating patients with repeat endoscopy lowered the overall complication rate. When repeat endoscopic intervention failed, subsequent salvage surgery did not result in worse outcomes than immediate surgery for rebleeding. Such results require a team approach, prompt recognition of recurrent bleeding, and rapid intervention when indicated.

A patient with a visible, nonbleeding vessel at endoscopy presents one of the greatest challenges in the management of bleeding peptic ulcer disease. These are at high risk of repeat bleeding, although such bleeding will occur in only a minority of these patients. In addition, older patients with large posterior duodenal ulcers and patients who present in shock are at an even higher risk for recurrent hemorrhage after observation or endoscopic treatment *(9)*. Two surgical strategies exist for patients in these groups: early elective operation versus operative intervention only if further bleeding is documented. The rationale for early elective surgery stems from data in the 1980s demonstrating a reduction in mortality from 43 to 7% when patients older than 60 years underwent operation after 4 versus 8 U of blood transfusion *(10)*. More recent trials fail to demonstrate convincing mortality reduction from early elective surgery, but higher rates of operation are seen *(11)*.

The best practice for management of patients with hemorrhage from peptic ulcer disease varies from hospital to hospital depending on the resources and expertise available in the treating institution. The best approach requires close collaboration between the medical and surgical care providers in each institution. For example, an attempt at repeat endoscopic therapy appears justified in hospitals with 24-hour access to experienced therapeutic endoscopists, but early surgery would be best if this is not the case. Moreover, repeated attempts at endoscopic control may not be prudent in elderly or seriously ill patients, in whom defini-

Table 2
Strengths and Weaknesses of Surgical Options for Treatment of Bleeding Duodenal Ulcers

Operation	*Arguments for*	*Arguments against*
Truncal vagotomy, pyloroplasty, and oversewing of bleeding vessel	Technically easy Rapid operation	Some incidence of dumping Moderate recurrence rate
Highly selective vagotomy and oversewing of bleeding vessel	Least physiologic derangement Lowest incidence of dumping	Technically difficult, longer operation Moderate recurrence rate
Antrectomy and truncal vagotomy	Most definitive ulcer operation	Highest surgical mortality Large operation Dumping syndrome Highest complication rate

tive control of hemorrhage is paramount for achieving a good outcome. In these patients, a surgical approach to ulcer rebleeding may be most appropriate. Our approach to the management of upper GI hemorrhage is outlined in Table 2.

Once surgical intervention becomes necessary, the operating surgeon has two goals: definitive control of the hemorrhage and treatment of the patient's ulcer diathesis. Because the surgical treatment of gastric and duodenal ulcers is different, and because the appropriate operation will depend on the patient's clinical situation, no single operative approach can be applied to all patients. The location of the ulcer, the cause of the patient's disease, a history of chronic ulcer symptoms, the patient's comorbidities, and the stability of the patient in the operating room all influence the surgeon's judgment.

Three acceptable surgical options for the treatment of a bleeding duodenal ulcer are listed in Table 2, in order of ascending magnitude of operation. In general, the most rapid operation is most appropriate for patients with hemodynamic compromise. However, whenever possible an acid-reducing procedure should be performed. Two randomized prospective studies have shown an increased incidence of recurrent bleeding and subsequent mortality in patients treated with oversewing of the bleeding vessel alone *(6,12)*. For these reasons, vagotomy and pyloroplasty is the operation of choice in unstable patients. In a stable patient, oversewing of the bleeding vessel combined with highly selective vagotomy may be more appropriate. Antrectomy with vagotomy is reserved

for patients who have rebleeding after another surgical procedure or significant gastric outlet obstruction.

The treatment of gastric ulcers differs from duodenal ulcers because most gastric ulcers are not associated with a high acid output. In addition, up to 10% of gastric ulcers may be caused by malignancy. The standard treatment of bleeding gastric ulcers is excision of the ulcer either by wedge gastric resection or partial gastrectomy, depending on the location of the ulcer within the stomach. It should be remembered that ligation of the bleeding vessel through a gastrotomy to control ongoing hemorrhage should be done before proceeding with resection. The gastric resection can then be carried out once the patient is stabilized. Oversewing of the bleeding vessel with biopsy of the ulcer to rule out malignancy is an acceptable alternative in some circumstances including ulcers at or near the esophageal-gastric junction. Ulcers located in the prepyloric or pyloric channel of the stomach, like duodenal ulcers, are associated with excess acid secretion, and a vagotomy is added to the operations for these ulcers.

GASTROESOPHAGEAL VARICES

Gastroesophageal varices are the most significant acute complication of portal hypertension. In the United States, cirrhosis secondary to alcohol overuse and viral hepatitis are the leading causes of portal hypertension and varices. Approximately 50% of cirrhotic patients have varices and are at risk for hemorrhage. Depending on the patient population, bleeding from gastroesophageal varices represents the second or third most common cause of acute upper GI bleeding in most series. Variceal bleeding is often massive, and the overall mortality approaches 30% *(13)*. In addition, variceal bleeding often recurs after an initial controlled episode; up to 70% of untreated patients rebleed within 1 year. The management of patients with varices is complicated by the underlying liver dysfunction associated with cirrhosis, including coagulopathy that may contribute significantly to hemorrhage. Treatment of patients with bleeding gastroesophageal varices requires control of the initial hemorrhage and stabilization of the patient hemodynamically. This section focuses on the initial management. The long-term management of the patient, to decrease the risk of subsequent hemorrhage, is a topic beyond the scope of this chapter.

The patient must be fully resuscitated and stabilized before invasive procedures are undertaken. Adjunctive drug therapy with either octreotide or vasopressin and nitroglycerin should be initiated while awaiting definitive endoscopy when the diagnosis of variceal bleeding

is strongly suspected. Either of these pharmacologic therapies can effectively arrest variceal bleeding in 50–70% of patients. Octreotide is preferred over vasopressin, as it is associated with a lower complication rate *(14)*. Unstable patients, despite fluid resuscitation and drug therapy, and patients with bleeding sufficient to obscure examination of the varices with an endoscope may require balloon tamponade (i.e., Sangstaken-Blakemore tube). Balloon tamponade with a Sangstaken-Blakemore or related tube is effective at temporarily controlling bleeding in up to 85% of cases. However, it is associated with significant complications and mortality, can only be used for brief (<24 hours) periods, and has a very high rebleeding rate when the balloon is deflated *(15)*. For these reasons, it is only a temporizing measure until another therapy can achieve definitive hemorrhage control.

Once stable, upper GI endoscopy is urgently performed to confirm the diagnosis and to treat the varices. In many series, up to half of patients with known varices will have another cause for the upper GI hemorrhage. Endoscopic therapy, either variceal ligation or sclerotherapy, is the primary treatment for actively bleeding esophageal varices *(14)*. This therapy is successful in controlling active bleeding in 80–95% of cases. Endoscopic variceal ligation is currently favored over sclerotherapy as it is at least as effective and is associated with a lower complication rate *(16)*. In 10–15% of patients, endoscopic and pharmacologic therapy will be unsuccessful at controlling either the initial hemorrhage or because of rebleeding within 48 hours. These patients require a procedure to reduce their portal pressures and may benefit from surgery to ablate their varices.

The role of the surgeon in the management of acute variceal hemorrhage is to achieve definitive control of life-threatening bleeding, while avoiding complications such as hepatic encephalopathy, and then to prevent future episodes of bleeding. Historically, surgical procedures to decompress portal pressure by shunting blood into the systemic circulation represented the definitive treatment for variceal bleeding secondary to portal hypertension. However, these procedures are high-risk operations, especially in the emergency setting. Mortality rates of 20–50% are reported in the literature *(17)*. Portal systemic shunting does nothing to address the underlying hepatic dysfunction in cirrhotic patients, and in many cases, hepatic function is worsened when blood is shunted away from the liver. With the advent of the widespread use of liver transplantation for the management of end-stage liver disease and the development of the transjugular intrahepatic portocaval shunt (TIPS procedure), the role of emergent surgical decompression has changed dramatically.

Three types of interventions currently exist for persistent variceal bleeding resistant to endoscopic and pharmacologic treatment: (a) TIPS; (b) portal systemic shunting; and (c) nonshunt devascularization procedures. Both TIPS and emergency surgical intervention are highly effective (90–95%) at controlling bleeding *(18)*. TIPS is a minimally invasive method of establishing a portosystemic shunt without surgery. It is associated with fewer complications than shunt surgery but appears to be a less durable solution, with 1-year shunt failure rates between 31 and 80% reported *(19)*. Currently, TIPS is used as a bridge to transplantation but is not considered definitive for patients who are not liver transplantation candidates.

A variety of operations have been used for surgical decompression of portal hypertension and control of variceal bleeding. These operations fall into three broad categories: total portal-systemic shunts, selective portal-systemic shunts, and devascularization procedures. Total portal-systemic shunts divert the vast majority of portal blood flow away from the liver. They are highly effective at decreasing portal pressure and managing bleeding but are associated with significant rates of hepatic encephalopathy and may worsen liver function. Selective shunts either partially decompress the portal circulation or isolate the gastroesophageal junction from high portal pressures. They preserve some portal blood flow, are associated with lower rates of encephalopathy, and may help preserve hepatic function. They are the most difficult surgical procedures to perform. The nonshunt procedures ligate varices without affecting portal hypertension. They are the only effective alternative for patients with portal venous thrombosis but have higher recurrence rates since collateral vessels develop. The advantages and disadvantages of the various procedures are discussed in Table 3. In general, total shunts or devascularization procedures are performed in the emergency setting because the more complicated selective shunts require longer operative times.

The appropriate treatment option in a given patient will depend on the patient's hepatic function (Childs-Pugh class) and whether the patient is a liver transplant candidate. In patients who are transplant candidates, the best management option for emergent bleeding control is a TIPS procedure. This is because any surgical procedure, particularly a shunt operation involving a portal dissection, will significantly complicate the patient's liver transplant operation *(20)*. Because liver transplant represents the definitive therapy for patients with end-stage liver disease, all efforts should be made not to complicate this treatment. In patients who are not liver transplant candidates, the appropriate choice of TIPS or surgical shunt will depend on the patient's hepatic reserve.

Table 3
Surgical Options for Treatment-Refractory Bleeding from Gastroesophageal Varices

Class of procedure	*Operation*	*Arguments for*	*Arguments against*
Total shunt	Direct portocaval shunt	Easy to perform	Postoperative encephalopathy Involves portal dissection
	Interposition mesocaval shunt	Avoids portal dissection	Shunt thrombosis Postoperative encephalopathy
Selective shunt	Distal splenorenal (Warren)	Low postoperative encephalopathy rate Avoids portal dissection	Technically difficult Worsens ascites
	Interposition portocaval (Sarfeh)	Low postoperative encephalopathy rate	Shunt thrombosis Involves portal dissection
Nonshunt devascularization	Esophageal transection and gastric devascularization (Suguira)	Easy to perform Low operative stress Only option with portal thrombosis	High recurrence rate

Childs-Pugh Class C cirrhotic patients have a very high operative mortality with emergency shunt surgery and a limited life expectancy secondary to their liver failure. Because of lower procedural mortality, these patients should be managed with TIPS. Childs-Pugh Class A and B cirrhotic patients have a significantly lower operative mortality and longer life expectancy than Childs-Pugh Class C patients. In these patients, the increased durability of surgical shunts relative to TIPS is worth the higher procedural morbidity and mortality of surgery. Patients who are not transplant candidates but have good liver function should have their refractory acute variceal bleeding controlled by emergency shunt surgery. This approach is outlined in Table 3.

DIEULAFOY'S LESION

Dieulafoy's lesion is an uncommon but significant cause of serious upper GI bleeding. It is characterized by the presence of an unusually large submucosal artery that lies close to the mucosal surface, which develops ulceration and arterial bleeding. Although found throughout the GI tract, the vast majority originate in the stomach and duodenum. This lesion is reported to be the etiology of upper GI hemorrhage in 1–5% of patients. The initial management of the lesion is resuscitation and rapid upper endoscopy. The lesion is notoriously difficult to diagnose at endoscopy, with only 63% found at initial endoscopy in one recent series *(21)*. Repeat endoscopy will identify the lesion in many patients in whom bleeding continues and is clearly indicated since the lesion is notoriously difficult to locate at the time of surgery if it is not actively bleeding. Initial management of these lesions can be accomplished endoscopically by injection or coagulation, with reported success rates of 85–95% *(22)*. Surgery is required when endoscopic therapy fails. Wide wedge excision of the gastric wall is the recommended surgical therapy, and this can be accomplished by either an open or laparoscopic approach. An important issue in the surgical management of these lesions is localization of the lesion. Because they are impossible to feel from the outside of the stomach, marking of the lesion by endoscopic injection of India ink preoperatively is a critical step in their surgical management.

MALLORY-WEISS SYNDROME

Mallory-Weiss syndrome or tears are linear gastric and esophageal mucosal tears at or just proximal to the gastroesophageal junction. It is caused by forceful retching or coughing, which causes a transgastric pressure gradient and leads to dilation and mucosal tearing of the

gastroesophageal junction. It is a common cause of upper GI bleeding accounting for approximately 5% of cases. In more than 90% of cases, the bleeding stops spontaneously *(23)*. As with other causes of upper GI bleeding, the initial management is resuscitation followed by upper endoscopy. At the time of endoscopy, fewer than 25% of patients are actively bleeding, and endoscopic hemostasis is successful in 90% of cases *(24)*. In noncirrhotic patients who fail endoscopic therapy and have evidence of ongoing bleeding, surgery is indicated for bleeding control. The procedure of choice is a gastrotomy with oversewing of the bleeding tears, a procedure that is very successful at controlling bleeding. Rebleeding is rare in the absence of cirrhosis. In cirrhotic patients, the appropriate management is directed at treating their portal hypertension, and the mortality rate is significant.

NEOPLASMS OF THE ESOPHAGUS, STOMACH, AND DUODENUM

Several benign and malignant tumors of the stomach can present with upper GI bleeding. Most often, bleeding is occult or limited, but some patients may present with life-threatening hemorrhage that will require emergent endoscopic or surgical treatment. GI stromal tumors, formerly referred to as leiomyomas and leiomyosarcomas, frequently present with upper GI bleeding. Gastric carcinoma and malignant gastric lymphoma may present as a bleeding gastric mass or ulcer. If the acute hemorrhage is controllable, the tumor should be appropriately staged and treated as if it presented without hemorrhage. If medical and endoscopic management is unsuccessful, surgical intervention is required. Both palliative and curative resections of the stomach are indicated. Surgical ligation of the bleeding vessel alone is not recommended but can be lifesaving in patients with tumors that are surgically unresectable.

SUMMARY

Acute upper GI bleeding is a common and important problem with a significant mortality rate. It is a problem found mostly in elderly patients with significant comorbid diseases. The management of this problem requires the multidisciplinary collaboration of primary care physicians, gastroenterologists, and surgeons. The initial management requires aggressive replacement of the patient's blood loss and rapid upper GI endoscopy to identify the disease process causing the hemorrhage. The primary management of most cases is endoscopic therapy with supportive medical management. The role of the surgeon is to obtain definitive hemorrhage control when endoscopic therapy fails. However, delays in

instituting surgical therapy often result in poor outcomes. It is critical to obtain surgical input early in the treatment course to ensure the optimal timing of potentially lifesaving surgical intervention.

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III Lower Gastrointestinal Bleeding

9 Infectious and Inflammatory Causes of Acute Gastrointestinal Bleeding

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CONTENTS

INTRODUCTION

Most patients who present to their physician with a sudden onset of diarrhea have a benign, self-limited illness. Bloody diarrhea, on the other hand, requires a thoughtful and thorough evaluation. Infectious colitis and inflammatory bowel disease (IBD) may present in similar patterns. Both are inflammatory colitides that cause a significant alteration in bowel habits along with protean complaints. A careful history and physical exam followed by appropriate diagnostic studies will most often distinguish between the two such that appropriate treatment can then be initiated.

Infectious diarrhea maybe divided into two syndromes based on the pathogenesis: inflammatory (or bloody) diarrhea and noninflammatory (or watery, nonbloody) diarrhea. We limit our discussion here to the inflammatory causes, which would result in significant bleeding.

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The IBDs are a group of chronic inflammatory disorders of the gastrointestinal (GI) tract of unknown etiology. The two that are associated with bleeding are ulcerative colitis and Crohn's disease. Ulcerative colitis involves inflammation in the mucosa and submucosa and is confined to the colon and rectum. Crohn's disease, in contrast, can affect any part of the GI tract from mouth to anus and is characterized by transmural inflammation from the mucosa through to the serosa. Depending on the severity of the inflammation, either condition may present with bleeding.

Although many patients with Crohn's disease or ulcerative colitis may present with GI bleeding, massive bleeding is rare. A recent epidemiologic study by Pardi et al. *(1)* identified patients with major acute hemorrhage, defined as hematemesis, hematochezia, or melena with hemodynamic instability (hypotension or orthostatic change in vital signs) and/or an acute decrease in hemoglobin concentration of at least 2 g/dL compared with baseline. Of 1739 patients with massive hemorrhage, only 31 (1.8%) had bleeding caused by IBD. During the same time interval, 4593 patients were hospitalized with IBD; massive hemorrhage occurred in 1.3% of these admissions. Of these patients, endoscopy (upper and/or lower) was helpful in most patients, with a few requiring angiography or labeled red blood cell scans to localize the bleeding source.

It is important to keep in mind that the differential of acute bloody diarrhea includes other processes such as superior mesenteric artery/superior mesenteric vein thrombosis with mesenteric ischemia, ischemic colitis, or a drug-induced colitis [gold, methyldopa, nonsteroidal anti-inflammatory drugs (NSAIDs)], which are discussed in other chapters of this book.

PATHOPHYSIOLOGY

Although infectious diarrhea is acquired predominantly through oral ingestion of pathogenic microorganisms, the etiology of IBD is not known. Symptoms of an infectious colitis can occur secondary to the direct effect of the organism on the mucosa, or those toxins produced by microorganisms. Nonetheless, the pathogenesis of infectious colitis (to a degree) as well as that of IBD is predominantly immune-mediated. For the symptoms of bloody diarrhea to occur, certain host defense factors must be overcome. These include (a) gastric acid, whose low pH is lethal to many organisms; (b) intestinal motility, which makes adherence to the intestinal mucosa more difficult; and (c) gut-associated lymphoid and systemic immune mechanisms, which provide specific cellular and humoral defense *(2)*.

Enterocyte damage and cell death is caused by the host-microorganism interaction. This interaction stimulates an inflammatory response by which various cytokines and inflammatory mediators are released. These mediators disrupt normal function and architecture (villous-crypt units), which include absorption and secretion. The villi line the small intestinal mucosa and absorb water and nutrients. Crypts are undifferentiated cells that lie beneath the mucosal surface in the submucosa. Crypt cells normally function to secrete fluid and electrolytes. Microorganisms or unknown triggers, as in IBD, may initiate an inflammatory response in which the surrounding neutrophils cause crypt abscess formation. Brush border damage occurs, and there is a subsequent loss of any effective digestive or absorptive surface. Ultimately, villous shortening and atrophy occur and, via T-cell lymphocyte activation, there is crypt hyperplasia.

Continued destruction of the epithelium results in ulceration, with exudates from the capillaries and lymphatics spilling into the lumen. This produces the clinical picture of bloody diarrhea.

CLINICAL PRESENTATION

In infectious diarrhea, symptoms will depend on the pathogenic properties of the organism involved. In IBD, the extent and severity of disease are the important factors. It is the chronicity of the patient's symptoms that will best help to distinguish infectious from idiopathic inflammation, as many features of the patient's history may be common to both conditions.

The setting in which the diarrhea develops is helpful in making a diagnosis. The history should include recent types of food eaten and places where food was obtained; presence of other affected individuals; recent travel history; recent antibiotic use or chemotherapy; recent hospitalizations; recent contacts with daycare centers, nursing homes, or mental institutions; and recent sexual contacts. Clearly the state of the host's immunity and underlying defense mechanisms must be considered, as impaired hosts are more susceptible to pathogenic GI infections. The presence of an immunocompromised state such as IgA deficiency, AIDS, steroid or immunosuppressive drug use, status post organ transplant, sickle cell disease, or neutropenic cancer patients may change the differential diagnosis.

The infectious inflammatory diarrheal syndrome is usually characterized by small-volume mucoid bloody stool rather than pure rectal bleeding. The bleeding component of the syndrome may be preceded by several days of watery diarrhea. Infectious causes of significant bleed-

Table 1
Infectious Agents Causing Acute Gastrointestinal Bleeding

Bacterial
Campylobacter
Clostridium difficile
Enterohemorrhagic *E. coli*
Salmonella
Shigella
Vibrio parahaemolyticus
Yersinia
Parasitic
Crytposporidium
Entamoeba histolytica
Viral
Cytomegalovirus
Herpesvirus

ing along with diarrhea include *Salmonella*, *Shigella*, *Campylobacter*, enterohemorrhagic *E. coli*, enterinvasive *E. coli*, *Clostridium difficile*, *Entamoeba histolytica*, and *Yersinia*. Bleeding can also occur from viral agents, most commonly cytomegalovirus (CMV), which causes discrete ulcerations, herpes simplex virus (HSV), and human papillomavirus (HPV), which result in mass lesions that may bleed secondary to friability and trauma (Table 1).

The clinical features of infectious colitis can vary with the affected area of the GI tract. Organisms that are found in the colon cause lower abdominal pain, tenesmus, and mucoid bloody stool. Toxins and microorganisms that attack small bowel enterocytes cause crampy diffuse periumbilical pain and large volume (>1 L/day) watery diarrhea without tenesmus.

In IBD, symptoms are usually chronic, although bloody diarrhea may bring the patient to a physician's attention. Bloody diarrhea is a predominant symptom in approximately 10–46% of patients with Crohn's disease *(3)*, but most patients with ulcerative colitis have bloody diarrhea. Acute life-threatening lower GI bleeding is reported in 6–10% of those emergency surgical resections for ulcerative colitis but in only in 0.6–2% for Crohn's disease *(4,5)*. As part of the history, it is helpful to know whether the patient has a family history of IBD, as well as smoking status. Patients who recently quit smoking are at higher risk for increased disease activity in ulcerative colitis; patients with Crohn's disease tend to be smokers more often than the normal population *(6)*.

Ulcerative colitis typically begins in the rectum and extends proximally. Symptoms tend to develop gradually, with the predominant symptom of diarrhea, accompanied by blood. Occasionally it may begin with infrequent stools but pure rectal bleeding, secondary to the significant rectal inflammation, resulting in a functional right-sided constipation. The course is usually chronic, characterized by remission with intermittent episodes of relapse *(7)*. Less commonly, the course may be continuous, with unrelenting symptoms and eventual surgery. The severity of the symptoms tends to parallel the severity of the inflammation, not necessarily the extent. In other words, a limited extent does not guarantee a more benign course. Symptoms range from occasional rectal bleeding even without diarrhea to profuse purulent bloody diarrhea. Patients may experience lower abdominal pain, urgency, tenesmus, and incontinence. With more severe inflammation, patients also have systemic complaints such as decreased appetite, weight loss, malaise, fatigue, weakness, or fevers. Extraintestinal manifestations of ulcerative colitis and Crohn's disease include arthralgias, skin rashes (pyoderma, gangrenosum, erythema nodosum), and uveitis.

In contrast to ulcerative colitis, in which diarrhea and bloody stools are present early in the disease, patients with Crohn's disease may have a less dramatic presentation, and the symptoms may be insidious. Patients may have vague abdominal pain and intermittent diarrhea for years before the diagnosis of Crohn's disease is considered. The predominant symptom usually correlates with disease location. In isolated small bowel disease (30% of patients with Crohn's disease), blood loss is usually occult *(3)*. Forty percent of patients have ileocecal disease at initial presentation and have pain and diarrhea but rarely significant bleeding. Fortunately, acute hemorrhage is rare in patients with small bowel disease.

Twenty-five percent of patients with Crohn's disease have involvement limited to the colon. It is this group of patients that will present with symptoms similar to those of ulcerative or infectious colitis. Patients complain of abdominal pain, fever, weakness, and hematochezia. Again, the diarrhea may be associated with urgency, tenesmus, and incontinence. The presence of perianal disease (anal structuring, perirectal abscess, fistula formation) should alert the clinician to the distinct possibility of Crohn's disease.

The physical exam varies with the severity of the bleeding and its effect on the patient but will most likely be nonspecific. In mild cases of colitis, the physical exam may be unremarkable. In severe cases, fever, tachycardia, and pallor are consequences of dehydration, blood loss, and malnutrition. Mucous membranes may be dry and skin turgor

diminished. An abdominal exam will determine tenderness or signs of peritonitis. Bowel sounds range from hypoactive (absence of peristalsis in toxic dilation) to hyperactive. A distended abdomen is of concern for toxic megacolon. Inflammatory masses may be palpable and suggestive of ileocecal Crohn's disease. A detailed perianal and rectal exam should be performed to assess for large skin tags, fistulae or abscess, mass lesions, and the gross appearance of stool. Other features that should be noted are the presence of oral ulcers, ocular inflammation, or skin lesions. These are systemic manifestations of certain infectious organisms or IBD.

DIAGNOSIS

It is important to remember from the outset that infectious causes of bleeding can be superimposed on an established or previously undiagnosed case of IBD. If a patient does not appear to be responding to appropriate therapy, alternative diagnoses must be sought. Routine laboratory tests such as a complete blood count and serum chemistries are generally not helpful in establishing a diagnosis but are important in the assessment of the severity of the disease. Abnormal chemistries may reflect a state of dehydration. More chronic disease processes can be manifested by hypomagnesemia, hypocalcemia, and a prolonged prothrombin time secondary to vitamin K malabsorption.

An elevated white blood cell count is nonspecific. The differential may be helpful if the eosinophil count is elevated, in suggesting an infectious etiology. The presence of anemia is seen with massive acute blood loss and is not helpful for diagnosis. An abnormal mean corpuscular volume (MCV), however, may suggest either iron deficiency (decreased MCV) or chronic malabsorption of B12 or folate (increased MCV). Acute-phase reactants such as C-reactive protein, erythrocyte sedimentation rate, ferritin, and platelets again may be elevated but are nondiagnostic.

As part of the initial workup, blood as well as stool cultures should be obtained, as occasionally blood cultures are positive for *Salmonella* organisms. Diagnostic stool studies should be focused as suggested by the patient's history and physical exam. If gross blood is not present at the time of physical exam but only by history, stool should be tested for occult blood. When stool is sent for routine enteric pathogen culture, most microbiology labs test only for *Salmonella*, *Shigella*, and *Campylobacter*. *E. coli* O157:H7 requires special MacConkey's media for diagnosis and if suspected must be specifically requested. Since *Yersinia* is easily missed on the culture plate, this also must be specifi-

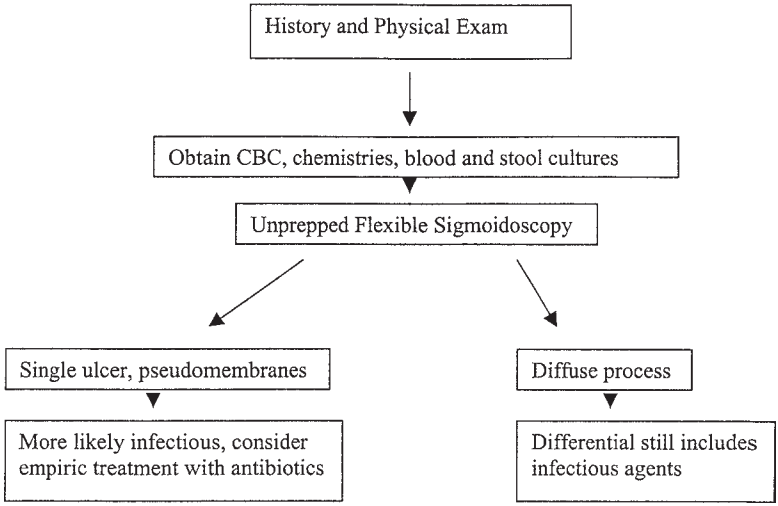

Fig. 1. Algorithm for workup to rule out infectious or inflammatory bowel disease. CBC, complete blood count.

cally requested of the laboratory. To rule out *C. difficile*, a separate stool sample should be sent for *C. difficile* toxin assay. Microscopic stool evaluation for ova and parasites should be obtained, but in most cases this will have a low yield.

In immunosuppressed patients, diagnostic testing may be expensive and have a low yield. Because no specific therapy exists for many of these diarrheal illnesses, the workup should focus on treatable causes that result in significant bleeding. *C. difficile* and CMV are the most common in this scenario *(8)*.

A flexible sigmoidoscopy *without preparation* should be performed in patients with signs and symptoms of proctitis or colitis (Fig. 1). If performed gently, the information obtained will outweigh the risk of potentiating bleeding or perforation. Endoscopy allows for characterization of the mucosa, acquisition of biopsies, and aspiration of more stool. Examination of the mucosa may distinguish among infectious colitis, ischemic colitis, and IBD, although these disorders can have a similar endoscopic appearance. Colitis caused by significant inflammation from any one of many etiologies appears as focal patchy or segmental erythema, edema, loss of normal vascularity, erosions, or frank ulcerations with mucosal friability and/or spontaneous hemorrhage.

Discrete ulcers can be seen in the presence of IBD, CMV, HSV involving the rectum, microsporidia, or amebae. The presence of a single ulcer suggests either an infectious source or trauma (solitary rectal ulcer syn-

drome). The appearance of *C. difficile* infection may range from nonspecific changes in the rectum to the characteristic pseudomembranous exudative colitis. *E. coli* O157:H7 tends to mimic ischemic colitis, with patchy erythema, mucosal hemorrhage, and edema *(9)*.

Ulcerative colitis may appear as mucosal edema, erythema with a loss of the vascular pattern, ulcerations, granularity, friability, spontaneous bleeding, mucopus, and mucosal detachment in a continuous pattern. Crohn's disease often spares the rectum and has skip areas. It classically appears as scattered apthous ulcers in mild disease or discrete, deep, longitudinal ("bear claw") ulcers with interspersed normal mucosa in more severe disease. The presence of pseudopolyps or the loss of normal haustral folds suggests chronic inflammation.

TREATMENT

Initial treatment for either infectious colitis or IBD should be supportive. The immediate goals of therapy include restoring any volume loss and preventing any further dehydration. Patients with only mild symptoms may be managed conservatively at home with oral fluid-electrolyte rehydration solutions and directed medical therapy. Hospitalized patients with major volume and blood loss may require blood transfusions in addition to intravenous fluids. If patients exhibit evidence of malnutrition and chronic disease, intravenous parenteral nutrition may be beneficial.

Medical Therapy

Once the patient has been assessed and stabilized, directed medical therapy can be initiated. For those patients stable for outpatient management, empiric antibiotics may be a reasonable modality. Empiric steroids to treat IBD may be detrimental until stool cultures are final, as immunosuppression may potentiate worsening disease.

For those patients with either a high suspicion or proven infection, antibiotics or simple supportive care may be adequate. Table 2 outlines antibiotic treatments for different agents causing colitis *(10)*.

For patients found to have inflammatory bowel disease, medical options are dependent on the type (Crohn's disease or ulcerative colitis), the extent, and the severity of disease. Table 3 outlines medical options for treating both ulcerative colitis and inflammatory Crohn's disease. For patients with suspected IBD who require hospitalization, consultation with both a gastroenterologist and surgeon are appropriate *(11)*.

Table 2
Medical Therapies for Various Infectious Causes of Bleeding

Organism	*Antibiotic of choice*
Shigella	Ampicillin 500 mg po qid × 5 d
Clostridium difficile	Metronidazole 500 mg po tid × 10 d
Amebiasis	Metronidazole 750 mg po tid × 10 d; then iodoquinol 650 mg po tid × 20 d
Campylobacter	Erythromycin 250–500 mg po qid × 7 d
Yersinia	Ciprofloxacin 500 mg po bid × 3 d
E. coli	Trimethoprim-sulfamethoxazole (TMP-SMX): TMP 10 mg/kg/d and SMX 50 mg/kg/d × 5 d

Table 3
Medical Therapies for Inflammatory Bowel Disease

Ulcerative colitis
Mild to moderate disease
Oral therapy: mesalamine, sulfasalazine, olsalazine, balsalazide
Topical therapy: mesalamine, hydrocortisone suppository/enema/cream
Severe disease
Hospitalize with surgical consultation
Intravenous steroids (hydrocortisone or methylprednisolone)
Cyclosporine[a]
Crohn's disease (inflammatory vs. fistulizing disease)
Mild to moderate disease
Oral aminosalicylate, antibiotics or infliximab 5 mg/kg × 1
Moderate to severe disease
Prednisone or infliximab 5 mg/kg × 1
Severe to fulminant disease
Hospitalize and surgical consultation
Intravenous steroids, antibiotics, supportive care

[a]Should only be considered in patients who are not septic, under the careful supervision of an experienced gastroenterologist.

Surgical Indications

There are several indications for urgent surgery in patients with severe colitis, whether caused by idiopathic IBD or an infectious source: massive hemorrhage, toxic megacolon with potential perforation, acute colonic obstruction from stricture, and fulminant colitis unresponsive to medical therapy *(12)*.

Massive hemorrhage secondary to ulcerative colitis occurs in fewer than 1% of patients but accounts for 10% of urgent colectomies.

The rectum may be spared for future ileoanal anastomosis, but it is important to remember that approximately 12% of patients will have continued hemorrhage from the retained rectal stump following colectomy. This bleeding most often responds to topical therapy in suppository form *(13)*.

Fulminant colitis with continued bleeding, fevers, and diarrhea occurs in approximately 10% of patients with ulcerative colitis, and in some patients with *C. difficile*, *Shigella*, and *E. coli*. It can also occur, but is more uncommon, in *Campylobacter*, *Yersinia*, and *Salmonella* infection. Fulminant colitis can progress to toxic megacolon and perforation.

Medical therapy in ulcerative colitis has a success rate of 87–92%. Patients who fail medical management with intravenous steroids, antibiotics, and other supportive measures after 7–10 days are at risk for toxic colitis. Intravenous cyclosporine therapy may be effective in this subset of patients to prevent a colectomy *(14)*. However, in patients who are septic, cyclosporine is not a reasonable option, and surgery is unavoidable *(15,16)*.

Patients with Crohn's disease may have continued bleeding from aggressive transmural disease. If the patient continues to bleed after 24 hours of intravenous steroids and supportive care, further imaging is necessary to locate the source of bleeding. Because Crohn's disease can occur throughout the GI tract, nucleotide imaging or angiography may be necessary to visualize the source. Embolization is not recommended in this setting, and surgical resection of the affected site with either diverting ostomy or primary anastomosis is indicated.

SUMMARY

- Acute bleeding from either infectious colitis or inflammatory bowel disease can present in a similar manner.
- The presence of an infectious agent should not preclude the workup for IBD if the patient's history supports this as an additional diagnosis.
- A timely diagnosis is important for proper treatment strategies.
- Supportive care and early surgical consultation are important in severe cases.

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10 Acute Bleeding from Diverticulosis and Ischemic Colitis

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Contents

INTRODUCTION

Lower gastrointestinal (GI) bleeding is a common medical problem in the United States. Two common causes of such bleeding are diverticulosis and ischemic colitis. This chapter reviews the pathogenesis, diagnosis, and management of bleeding associated with these two conditions.

DIVERTICULAR BLEEDING

Diverticular bleeding is the most common source of lower GI bleeding, with severe hemorrhage occurring in 3–5% of patients with diverticulosis *(1,2)*. Bleeding ceases spontaneously in 70–80% of patients with diverticular bleeding. Rebleeding occurs 20–40% of the time *(3,4)*, and the chance of a third bleeding episode in such patients is 50% *(3)*. This has led some experts to recommend surgical resection after a second bleeding event.

Pathogenesis

Typical colonic diverticula do not contain all layers of the colonic wall, making these sacculations actually pseudodiverticula. Diverticula

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develop most often in the left colon, but diverticular bleeding occurs most commonly on the right side *(5)*. Colonic diverticula are intimately associated with blood vessels, and the resulting blood loss is usually arterial. The inciting factor for bleeding is unclear, but it appears to be related to thinning of the vasa recta within the diverticulum. Based on resected colon specimens, inflammation does not appear to play a role in diverticular bleeding.

Cardinal Symptoms and Signs

Symptoms

Patients with diverticular bleeding typically present with abrupt, painless bleeding, sometimes of large volume. This initial event can be followed by lower abdominal cramping, the urge to defecate, and the passing of dark red or purple clots and may be accompanied by hemodynamic instability manifested by rapid heart rate and lightheadedness.

Physical Examination

In general, the physical examination is unremarkable in patients with diverticular bleeding, but it may demonstrate mild low abdominal tenderness without peritoneal signs. On rectal examination, red blood or dark or purple clots may be found. Tachycardia or orthostasis may be present if significant blood loss has occurred.

Diagnosis

The differential diagnosis in patients passing red blood out the rectum includes ischemic colitis, arteriovenous malformation, inflammatory bowel disease, colon carcinoma, hemorrhoids, anal fissure, and brisk upper GI tract bleeding.

A focused history and physical examination is the first step in managing patients with diverticular bleeding. Initial laboratory studies should include a complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), creatinine, and type and crossmatching of blood. A normal initial hemoglobin and hematocrit value should be interpreted with caution since volume contraction may mask the actual degree of blood loss. An elevated BUN without a simultaneous rise in creatinine may be a clue pointing to an upper GI source of bleeding. A coagulation profile should be ordered in patients with a history of liver disease or bleeding problems, or in those on anticoagulants.

The diagnosis of diverticular bleeding can be made by colonoscopy, angiography, or nuclear scanning technique. Colonoscopy and preceding colonic purgation are safe in the setting of diverticular bleeding as

long as the patient is hemodynamically stable. There are no data to suggest that such colonic cleansing will reactivate or increase the rate of bleeding *(6)*. Colonoscopy can identify bleeding sites in up to 85% of these patients *(7)*, whereas the risk of a colonoscopy complication, such as perforation, is low even in the setting of acute lower GI bleeding *(7–10)*.

Another readily available diagnostic test, angiography, is considered by some experts to be the procedure of choice for diagnosing active diverticular bleeding. Angiography is specific and sensitive if bleeding is active and sufficient at a rate of at least 0.5–1 mL blood/min *(11)*. The superior mesenteric artery is usually studied first, as bleeding more commonly occurs in the right colon. This is followed by examination of the inferior mesenteric artery and, if necessary, the celiac axis. The diagnostic yield of angiography for lower GI bleeding ranges from 40 to 78% *(11–15)*. In four of these cited studies, diverticular bleeding was the most common cause of bleeding *(11–15)*. The risk of an adverse event with angiography in the setting of acute lower GI bleeding is 2–4% *(11–15)*, including contrast allergy, contrast-induced renal failure, or embolism from dislodged thrombus.

Nuclear scanning with ^{99M} Tc sulfur colloid or ^{99M} Tc-tagged red blood cells may be helpful in identifying a source of diverticular bleeding. This test is capable of detecting a slower rate of bleeding compared with angiography, down to 0.1 mL/min *(16)*. However, nuclear scanning has a low specificity, and there are conflicting data regarding its accuracy in identifying the actual anatomic site of bleeding. Nonetheless, given the very low risk of adverse events with nuclear scanning, some experts advocate performing this scan prior to angiography in hopes of better identifying a bleeding site. This can then be followed by angiography as a diagnostic and therapeutic modality.

Treatment

Most patients with diverticular hemorrhage stop bleeding spontaneously. Supportive medical care, volume resuscitation, and correction of any coagulation abnormalities should be addressed prior to any diagnostic evaluation. Hemodynamically unstable patients require monitoring in an intensive care unit. Patients with brisk lower GI bleeding, with or without hemodynamic instability, should have a nasogastric tube placed. The presence of large amounts of bile and the absence of blood makes an upper GI bleeding source unlikely.

Good hemodynamic status of patients must be achieved prior to proceeding with diagnostic testing and treatment. Hemodynamically unstable patients require fluid resuscitation, the primary end point of

which is euvolemia and stable vital signs. The need for red blood cell transfusion should be determined on an individual patient basis.

Colonoscopy, angiography, and surgery present therapeutic options to control diverticular bleeding. The role of colonoscopic therapy in acute diverticular bleeding is in evolution. Therapeutic options that can be delivered through the colonoscope to stop bleeding include thermal therapy (heater probe, Bicap probe) and injection therapy with epinephrine. Early studies *(17,18)* employing therapeutic colonoscopy reported a high hemostasis rate of up to 95%. Jensen et al. *(19)* reported their experience performing urgent colonoscopy for the diagnosis and treatment of diverticular bleeding. They identified patients with high-risk endoscopic findings (active bleeding, visible vessel) and used injection and/or thermal therapy to treat the source of bleeding. Ten patients were treated with therapeutic colonoscopy with no recurrent bleeding and without complications. Although the results of this study are encouraging, the patient population was small, raising questions regarding whether such results can be expected in general populations. Further studies should help to clarify the role of therapeutic colonoscopy for diverticular bleeding.

Angiography may also be performed to treat active diverticular bleeding. Extravasation of contrast material at angiography is consistent with active hemorrhage and, if identified, can be treated with either of two therapeutic options: selective injection of vasopressin into an artery or superselective embolization with gelatins or cellulose. Gomes et al. *(20)* compared vasopressin with embolization for active lower GI bleeding (including diverticular bleeding) and achieved a success rate of 70% for either vasopressin or embolization. Two other studies *(21,22)* found similar success rates for treatment with intraarterial vasopressin *(21)* and superselective embolization *(22)*. The complication rate for angiography is 2–4% *(12,14)* but may be as high as 17% with therapeutic applications *(20)*.

Surgery for acute diverticular bleeding is usually reserved for patients who have failed medical, colonoscopic, or angiographic therapy. If the bleeding site has been identified by colonoscopy or angiography, a segmental resection can be performed. In patients undergoing segmental resection of a previously identified bleeding site, the rebleeding rate is only 6% *(11)*. In patients with continued bleeding and no identified bleeding site, all segments of the colon with diverticula must be removed *(3,4)*, which usually requires a subtotal colectomy. An algorithmic approach to patients with suspected diverticular bleeding is shown in Fig. 1.

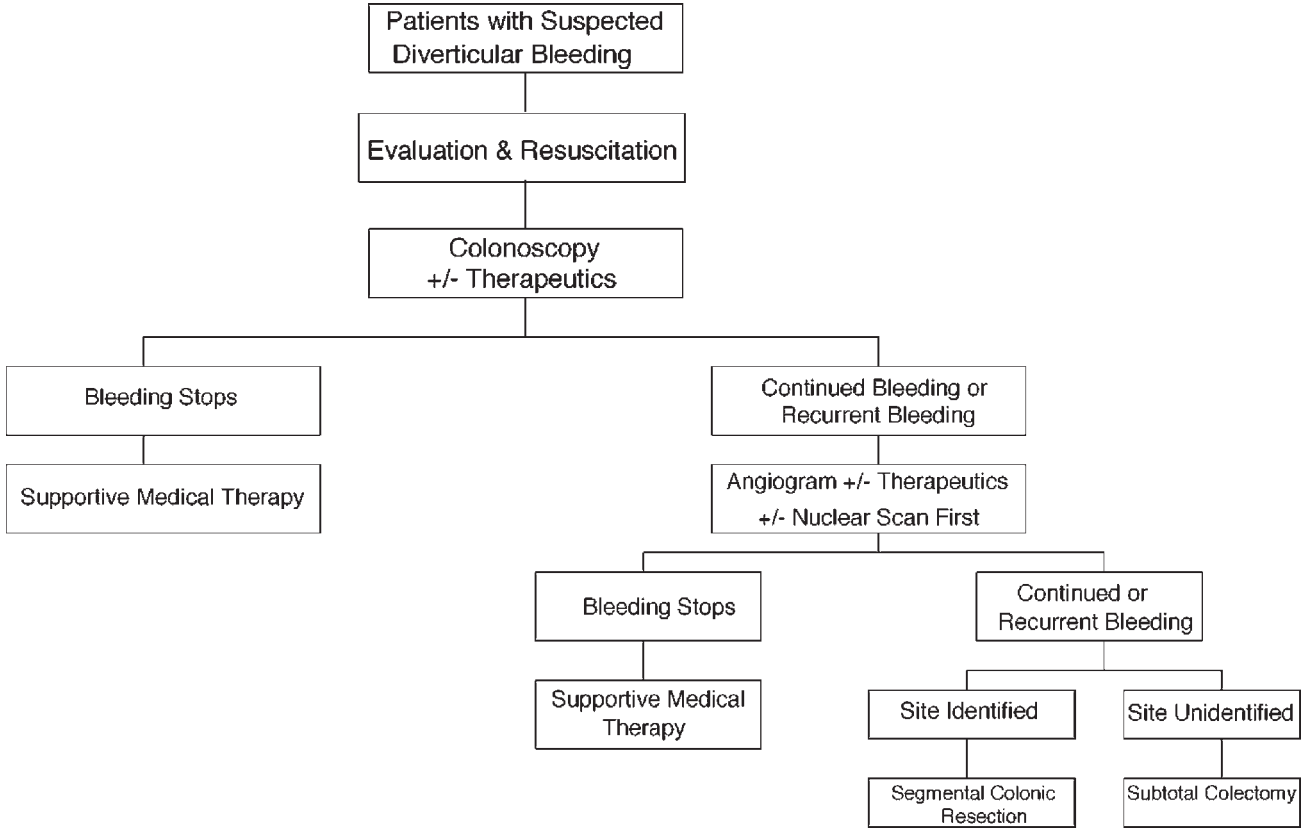

Fig. 1. Algorithm for treatment of diverticular bleeding.

Summary

Acute diverticular bleeding is the most common cause of lower GI bleeding. Most patients are otherwise asymptomatic at presentation, and bleeding ceases spontaneously 70–80% of the time. Initial evaluation includes history and physical examination, laboratory work, and fluid resuscitation. The administration of packed red blood cells should be based on individual patient needs. Colonoscopy and angiography can be used for diagnosis and treatment of diverticular bleeding. Surgical therapy is reserved for patients who fail to respond to colonoscopic or angiographic therapy. Preferably a segmental colonic resection is performed for a previously identified bleeding site, reserving subtotal colectomy for patients with ongoing bleeding from an unidentified site.

ISCHEMIC COLITIS

Colonic ischemia is the most common form of intestinal ischemic injury and exists as a spectrum of disorders: (a) reversible colopathy (submucosal or intramucosal hemorrhage); (b) transient colitis; (c) chronic colitis; (d) stricture; (e) gangrene; and (f) fulminant colitis *(23)*. The incidence of colonic ischemia is probably underestimated, since most patients have minimal disease and do not seek medical attention. This segment of our chapter reviews that spectrum of colonic ischemia that can cause acute lower GI bleeding. Accordingly, chronic ischemic colitis and its complications are not discussed.

Pathogenesis

The estimated incidence of colonic ischemia is 1:200,000 hospitalizations *(24)*, and it is a common disorder in elderly patients. The superior mesenteric artery supplies the proximal half of the colon, and the inferior mesenteric artery and branches of the iliac artery supply the distal half. The segments of the colon most susceptible to ischemic injury are the descending colon, sigmoid colon, and splenic flexure. Rectal ischemia is quite uncommon.

Anatomic factors such as luminal narrowing of the inferior mesenteric artery and lack of collaterals between the superior mesenteric and inferior mesenteric arteries may predispose patients to colonic ischemia. Physiologic factors such as low perfusion pressure, decreased colonic perfusion secondary to altered colonic motility, sustained mesenteric vasospasm associated with systemic hypotension, or other severe physiologic stress produced by sympathetic activity *(25–27)* also predispose patients to colonic ischemia. In most cases of clinically apparent colonic

ischemia, no cause is identified. When a cause is found, the more common identifiable reasons include atherosclerotic disease of the superior or inferior mesenteric arteries or their branches, cardiac failure, arrhythmia, hypotension, arterial embolus, and cholesterol emboli *(27)*.

Two other clinical situations deserve special mention. Colonic ischemia can be associated with both carcinoma of the colon and aortic surgery. Colonic ischemia associated with colon carcinoma typically occurs proximal to the tumor and may occur with or without obstruction *(28–30)*. Symptoms may be related to the colonic neoplasm or ischemia. Biopsies should be obtained, as colonic ischemia may masquerade as colon carcinoma. Colonic ischemia may also complicate aortic surgery. The incidence of colonic ischemia in this setting is as high as 7%, with as many as 60% of patients undergoing surgery for ruptured aortic aneurysm developing such ischemia *(31)*. Contributing factors in this setting include hypotension, arrhythmia, hypoxemia, and operative trauma to the colon.

The resultant morphologic appearance of colonic ischemia ranges from mild mucosal and submucosal hemorrhage and edema to severe transmural necrosis.

Cardinal Symptoms and Signs

Symptoms

Patients with acute colonic ischemia typically present with abrupt, crampy, mild abdominal pain, most often located in the left lower quadrant. This abdominal pain is accompanied by a sudden urge to defecate and the passing of bright red blood or dark clots. This bleeding of colonic ischemia is typically small in volume and generally does not require transfusion. Other associated symptoms include nausea, vomiting, diarrhea, and abdominal distention.

Physical Examination

Patients with ischemic colitis typically exhibit mild to moderate abdominal tenderness, usually corresponding anatomically to the affected colonic segment. About 10–20% of these patients have peritoneal signs *(24)*, probably representing some degree of transmural colonic necrosis. Other findings on physical examination may include low-grade fever, tachycardia, and abdominal distention.

Diagnosis and Treatment

The differential diagnosis of patients presenting with rectal bleeding includes diverticular bleeding, arteriovenous malformation, inflammatory bowel disease, colon carcinoma, hemorrhoids, anal fissure, and brisk upper GI tract bleeding.

Laboratory abnormalities are nonspecific and may include leukocytosis with a left shift and a prominent metabolic acidosis in patients with colonic necrosis. A wide range of further diagnostic testing is available, including plain abdominal X-rays, barium enema, colonoscopy, computed tomography (CT), and angiography. Abdominal X-rays typically show nonspecific bowel dilation, but the most specific finding of colonic ischemia is "thumb printing" from mucosal hemorrhage and edema. These thumb prints appear as multiple, round, smooth, soft tissue densities projecting into the air-filled colonic lumen *(24)*.

Barium enema was the first radiologic test used to diagnose colonic ischemia more definitively. Although not as sensitive as colonoscopy in diagnosing this condition, the sensitivity of barium enema approaches 80% *(32)*. The classic finding on barium enema is thumb printing; other possible findings include colonic ulcer, mural deformity, and sacculation *(32)*.

Subsequent to barium enema, colonoscopy has become the procedure of choice for diagnosing colonic ischemia. The advantages of colonoscopy over barium enema include greater sensitivity, direct visualization of the mucosa, and the ability to obtain tissue samples by pinch biopsy. Colonoscopy also is preferred over the simpler sigmoidoscopy since approximately 50% of ischemic lesions in the colon are proximal to the sigmoid colon *(24)*. Findings at endoscopy include hemorrhagic nodules, ulcers, mucosal erythema, edema, and friability. These findings are typically segmental, with the intervening mucosa being normal. If the colonoscopist finds mucosal changes suggesting necrosis (cyanotic gray or black mucosa), the procedure should be terminated owing to an increased risk of perforation *(33)*. Furthermore, colonoscopy in any setting of suspected ischemia should be performed with caution, utilizing minimal air insufflation, since overdistention of the colon could lead to diminished colonic blood flow and worsening of colonic ischemia *(34)*.

CT is not routinely used to investigate suspected colonic ischemia. However, there are potential abnormalities to be seen with CT scanning, including mucosal thickening, luminal narrowing, and intraluminal filling defects, none of which are specific to colonic ischemia. Finally, mesenteric angiography is rarely needed in evaluating patients with colonic ischemia. Usually by the time a diagnosis of colonic ischemia is made, restoration of normal blood flow has occurred. Angiography may be helpful when the patient exhibits more severe physical findings than are typical for common left colon ischemia and the diagnoses of acute mesenteric or right colon ischemia are being considered *(35)*.

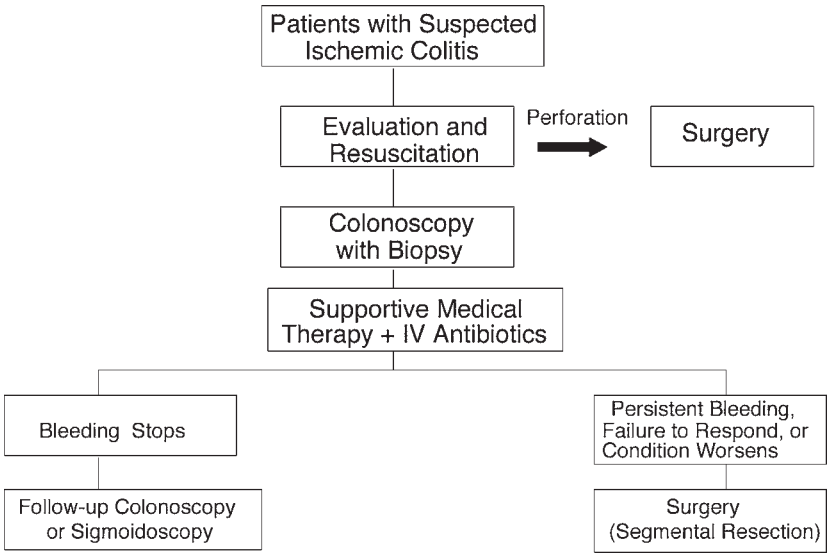

Fig. 2. Algorithm for treatment of ischemic colitis.

Once the diagnosis of colonic ischemia has been made and there is no suggestion of intestinal perforation or necrosis, the patient is usually managed conservatively *(34,36,37)*. Patients with intestinal perforation or necrosis require surgical evaluation and treatment, whereas those lacking these more ominous developments are managed with bowel rest and parenteral fluid and antibiotics. Broad-spectrum intravenous antibiotics have been shown experimentally to reduce the length and severity of bowel damage *(34,38,39)*. Finally, pulmonary and cardiac status must be optimized, and any medications that might worsen colonic ischemia should be avoided. A nasogastric tube and suction should be employed if an ileus is present.

In patients with ischemic colitis, symptoms most commonly subside within 24–48 hours, and clinical, roentgenographic, and colonoscopic evidence of healing is seen within 2 weeks *(36)*. No further therapy is generally needed in such patients, but follow-up examinations such as colonoscopy or sigmoidoscopy should be undertaken to document healing and exclude stricture formation *(24,37)*. In those patients who have persistent rectal bleeding, who fail to improve in a timely manner, or who worsen, early colonic resection is indicated to avoid the risk of colonic perforation and intraabdominal sepsis. The foregoing approach to patients with acute lower GI bleeding from suspected ischemic colitis is presented in Fig. 2.

Summary

Ischemic colitis is the most common form of intestinal ischemic injury, most often occurring in the left side of the colon. Contributing factors include atherosclerosis, cardiac failure, arrhythmias, and shock. Colonoscopy is the diagnostic procedure of choice since it allows direct visualization of the mucosa and tissue sampling. Management is usually merely supportive, consisting of bowel rest and intravenous fluid and antibiotics, with most patients recovering in 24–48 hours. Those with peritoneal signs require immediate surgical evaluation and probably surgical resection of necrotic bowel. Those who have persistent rectal bleeding, fail to respond to supportive therapy in a timely manner, or worsen need surgical resection to avoid colonic perforation and intra-abdominal sepsis.

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11 Radiation Proctopathy and Anorectal Diseases

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CONTENTS

INTRODUCTION

The anorectum is a frequent source of acute lower gastrointestinal (GI) bleeding, although in the vast majority of cases, bleeding is mild and self-limited. Possible etiologies include vascular lesions, mucosal trauma, inflammatory diseases, and neoplastic growths. Presentation ranges from spotty bleeding visible only on the toilet tissue to massive hemorrhage with orthostasis and anemia. Although the anorectum is relatively accessible, anorectal diseases are frequently misdiagnosed. One challenge is to distinguish the common trivial lesions from those that may be serious and to focus therapy and referrals as appropriate. This chapter discusses several common causes of anorectal bleeding but primarily highlights hemorrhoids, fissures, and radiation proctopathy.

The etiology of anorectal bleeding can often be determined after a focused history and physical examination. History should detail the onset, duration, and frequency of bleeding episodes. Many causes of anorectal bleeding such as hemorrhoids and fissures are recurrent, so

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previous confirmation of these diagnoses is helpful. Patients with a prior history of radiation therapy for prostate cancer or gynecologic malignancy are at increased risk for bleeding owing to the neovascular effects of radiation on the rectal mucosa. A history of cirrhosis, especially in patients with complications of portal hypertension, should raise the possibility of anorectal varices. The details of associated symptoms such as pain, pruritis, and prolapse may help to distinguish lesions such as hemorrhoids, solitary rectal ulcer, anal cancer, or anal fissure from one another. A change in stool caliber or a family history of colon cancer may suggest rectal carcinoma as a source of hematochezia. Urgency with or without diarrhea may suggest an infectious colitis or ulcerative proctitis, a subset of ulcerative colitis. A history of receptive anal intercourse in homosexual men or genital warts in either sex may raise the specter of an anal carcinoma. Patients should also be questioned about anorectal trauma. Digital manipulation related to constipation, pruritis ani or psychiatric disease, rectal foreign bodies placed for homoerotic purposes, or simple passage of a very difficult large stool may cause anal bleeding related to mucosal trauma.

The next step is a thorough anorectal examination. To perform a proper examination, step-by-step explanation, reassurance, and gentle technique will help to minimize patient discomfort and ensure an adequate and thorough examination. In the absence of a special table allowing the "jackknife" position, the patient should be placed in the left lateral decubitus position. The examination begins with inspection of the perineum. The buttocks, sacral region, and thighs are inspected for signs of pilonidal disease, dermatologic conditions, and infections. The buttocks are firmly retracted to permit inspection of the perineal region. Special attention is paid to the possibility of fistulous openings, fecal or mucus soiling, excoriations, or chronic skin changes, which may point to an underlying disease process. Anal tumors, skin tags, and external hemorrhoids are often identified at this point. This is also the best way to identify an anal fissure.

The anorectal examination then proceeds with the digital examination. Careful palpation of the perineal region can reveal induration, tenderness, or cords of fistulous tracts. The well-lubricated examining finger is then gently inserted into the anus. Some causes of acute anorectal bleeding may be exquisitely tender to digital rectal examination, often requiring the use of topical anesthetics or even examination under sedation. Sphincter tone should be evaluated with the patient relaxed, during voluntary contraction of the external anal sphincter and with bearing down. Internal examination is directed toward the palpation of polyps, tumors, feces, hemorrhoids, and foreign bodies.

A more detailed internal examination can be accomplished utilizing anoscopy, sigmoidoscopy, or colonoscopy, depending on the suspected etiology of bleeding. Most causes of hematochezia are anorectal in origin. Under the appropriate clinical circumstances (age of patient, character of bleeding, and other factors), the burden is on the clinician to rule out a rectosigmoid malignancy. Anoscopy is the best means of examining the anal canal. A variety of short, tubular metal or disposable instruments are available, with either built-in or external light sources. A removable obturator piece is held in place to permit insertion of the lubricated scope into the anal canal. The obturator core is removed to allow inspection of the mucosa. The rigid proctosigmoidoscope has essentially been abandoned in favor of the flexible fiberoptic or video endoscope. With this modality, excellent visualization of the mucosa can be obtained, and the instrument can be retroflexed 180 degrees just prior to removal to visualize the distal rectum and anal region. In addition, a variety of therapeutic modalities are available to the clinician using the flexible endoscope, including cautery devices, snares and biopsy forceps, rubber banding techniques, and so forth.

HEMORRHOIDS

Hemorrhoids are a common medical and surgical problem *(1)*. They are the cause of symptoms in a large portion of adults in the United States *(2,3)*, and estimates of prevalence range from 4.4% to as high as 50% of the adult population *(4)*. The peak age distribution for hemorrhoids is between age 45 and 65 years *(5)*. Internal hemorrhoids rank as the most common cause of self-limited bleeding in ambulatory adults *(6)*. Rarely, hemorrhoid bleeding can be quite severe, requiring urgent evaluation and therapy.

Pathophysiology

Despite the high prevalence of hemorrhoids, the exact etiology is still unclear. Detailed anatomic studies have demonstrated that sliding downward of the anal cushions is a likely etiology *(7)*. The anal cushions are composed of blood vessels, smooth muscle, and elastic connective tissue within the submucosa. Hemorrhoids are associated with straining and irregular bowel habits. Although it is commonly believed that constipation is an important risk factor for the development of hemorrhoids, other studies have suggested that diarrheal disorders are more frequently associated with hemorrhoidal disease *(8)*. Straining maneuvers related to diarrheal disease or constipation may cause engorgement of the anal cushions during defecation and tend to push the anal cushions out of the

Table 1
Classification of Internal Hemorrhoids

Type	*Characteristics*
First degree	Bulge into lumen of anorectal canal, but do not protrude out of the anus; may produce painless bleeding
Second degree	Prolapse out of the anus with defecation but reduce spontaneously
Third degree	Prolapse out of the anus with defecation or straining and require digital reduction
Fourth degree	Permanently prolapsed and are irreducible despite attempts at manual replacement

canal *(5)*. Repeated stretching of the smooth muscle causes disruption and prolapse *(7)*. Other theories suggest that hemorrhoids share similarities with arteriovenous malformations *(9)*. Another theory suggests that the primary abnormality in the development of hemorrhoids is defective support of overlying mucosa, known as the hypertrophic internal anal sphincter hypothesis *(2)*. The internal sphincter can become hypertrophic, and the anal outlet develops a functional narrowing. With straining maneuvers, the fecal bolus acts as an obturator, forcing the hemorrhoidal cushions to descend through the hypertrophic sphincter, enlarge, and become symptomatic.

Hemorrhoids may be either external or internal, and often both types are present in the same individual. External hemorrhoids develop from the dilated vascular plexus below the dentate line and are covered by squamous mucosa. Internal hemorrhoids arise above the dentate line, develop from the superior hemorrhoid plexus, and are covered by columnar epithelium. Internal hemorrhoids can be classified based on their degree of prolapse (Table 1). Rectal mucosal prolapse, although a far less common condition, may be confused with prolapsing internal hemorrhoids. Bleeding of prolapsing rectal tissue may develop because of mucosal trauma. The chronic straining and diarrheal disease that predisposes patients to hemorrhoids predisposes patients to rectal prolapse as well. In addition, trauma (surgical, obstetric, and so on) of the anal sphincter also predisposes patients to rectal prolapse. Hypertrophied anal papillae, which are usually asymptomatic, can sometimes protrude below the dentate line and be confused with a hemorrhoid. Finally, rectal polyps, neoplasms, perirectal abscesses, and anorectal varices must also be distinguished from hemorrhoidal disease.

Cardinal Signs and Symptoms

External hemorrhoids are often asymptomatic or only a minor nuisance. Anorectal bleeding is uncommon. External hemorrhoids can become symptomatic and exquisitely painful if they thrombose. Distention of the overlying perianal skin and the inflammation associated with thrombosis may cause significant discomfort. The typical presentation is that of abrupt onset of a small anal mass with pain that usually peaks within 48 hours. If the overlying skin becomes necrotic, bleeding or purulent discharge may follow. If hemorrhoids are left alone, pain usually subsides by the third or fourth day, and the thrombus becomes organized. Eventually anal tags may remain and other than causing minor pruritis or hygiene problems, are of little consequence. External hemorrhoids must be distinguished from an anal malignancy, prolapsed internal hemorrhoids, and anorectal varices.

Internal hemorrhoids often cause no symptoms, but when they do, bleeding is the most common reason to seek medical attention. Typically, patients describe occasional bright red painless bleeding at the end of defecation. Blood typically spots the toilet tissue during wiping but may drip into the toilet water or even squirt as a fine stream during straining. Rarely, acute immediate bleeding (implying rupture of a small vessel) may be severe enough to cause hemodynamic instability and require blood transfusions. Persistent frequent bleeding over the course of months or years may cause iron deficiency, but in a retrospective review, hemorrhoidal bleeding severe enough to cause anemia was seen in only 1 patient per 200,000 people per year in Olmsted County *(10)*.

Although a friable hemorrhoid may cause a positive fecal occult blood test, occult bleeding sufficient to produce anemia should not be attributed to hemorrhoids. Because hemorrhoids are so common in the general population, bright red rectal bleeding should not automatically be attributed to these common lesions. A flexible sigmoidoscopy or sometimes a full colonoscopy may be necessary to rule out inflammatory (i.e., ulcerative proctitis) or neoplastic lesions (polyps, cancer). Internal hemorrhoids may sometimes produce discomfort, pruritis ani, fecal soiling, or prolapse. Pain alone is not a typical symptom of internal hemorrhoids and may be a marker for other associated diseases such as anal fissure and abscess. Prolapsed hemorrhoids can produce symptoms ranging from mild discomfort and pruritis to significant pain associated with strangulation. If left untreated, strangulated hemorrhoids can become gangreneous, with associated abscess or sepsis. Immediate surgical management is essential to avoid this complication.

Treatment

The management of external hemorrhoids in most cases is conservative. Mildly symptomatic hemorrhoids and thrombosed external hemorrhoids can be managed with warm sitz baths two to three times per day. If patients are able, bed rest may help minimize swelling and aggravation of thrombosed external hemorrhoids. Agents that allow the passage of soft stools, such as psyllium seed preparations, synthetic mucilloids, and the sodium or calcium salts of dioctyl sulfosuccinate can decrease irritation of edematous and tender hemorrhoids. Topical agents containing anesthetic or steroid ointments may provide additional relief. Usually with a conservative approach, patients can be supported through the few days required for the resolution of symptoms.

Severe pain associated with acutely thrombosed external hemorrhoids may be treated surgically. The hemorrhoid is incised and the clot evacuated, promptly relieving pain. This should be performed, if necessary, within the first 48 hours of symptom onset, as the natural history is resolution in a few days. In addition, once an organized thrombus forms, it cannot be removed.

Treatment of internal hemorrhoids can also be managed with conservative measures initially. For most first- and second-degree hemorrhoids, bulk-forming agents, a high-fiber diet, and adequate fluid intake promote soft, formed stools that help reduce straining with defecation. These simple measures should not be underestimated because a surprisingly large number of patients will see substantial improvement in the frequency and amount of bleeding. Warm sitz baths and good anal hygiene may provide additional benefit. Topical anesthetic agents and short courses of topical steroids may provide short-term relief of pain, pruritis, and soreness.

If conservative measures fail, a variety of more directed approaches should be considered. Several techniques have been developed utilizing cautery, chemicals, banding, and even cold, but all have the goal of producing inflammation and subsequent fibrosis of hemorrhoidal and perihemorrhoidal tissues to prevent bleeding and prolapse. Banding and surgery have the additional benefit of removing redundant tissue. Rubber band ligation in the office setting to treat bleeding and prolapsing internal hemorrhoids successfully was first described 40 years ago *(11)*. This simple outpatient procedure requires no sedation. Through an anoscope, a hand-held rubber band ligator is used to place a band at the base of a hemorrhoidal cushion, taking care to place the band at least 5 mm above the dentate line (Fig. 1). One to four bands are applied per session, and sessions are repeated every 4–6 weeks as necessary *(12)*. Mild

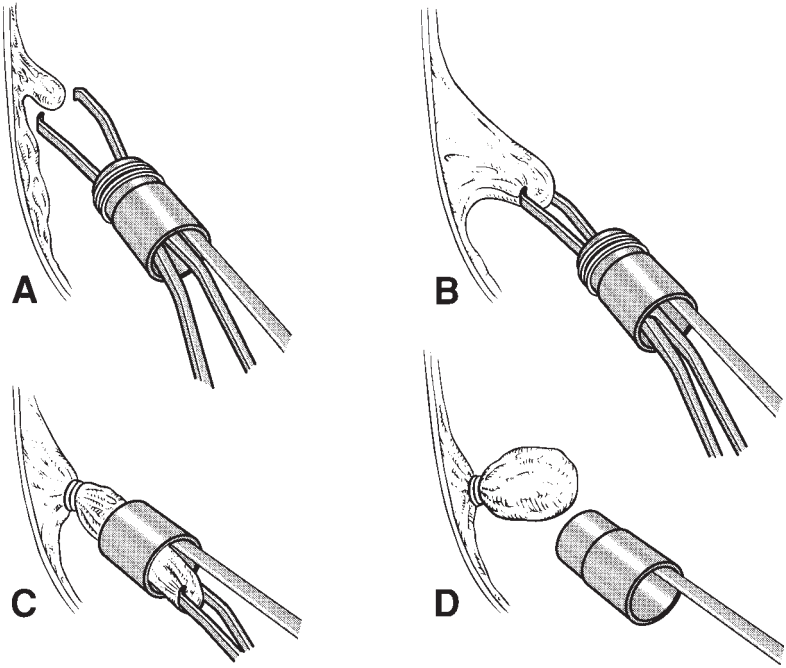

Fig. 1. (A–D) Rubber band ligation of an internal hemorrhoid. Band should be placed directly on, or preferrably just at, the proximal margin of the hemorrhoid. (Adapted with permission from ref. *2*.)

discomfort does occur in many patients and generally lasts for 5–7 days after application. Severe pain is a sign of infection or incorrect placement or migration of the band near the dentate line. Complications are rare but can be serious. Complications severe enough to warrant hospitalization were seen in 2.5% of patients in one large series *(13)*. Acute perianal sepsis is the most feared complication *(14,15)*. Important clues to infection are a triad of symptoms: delayed anal pain, urinary retention, and fever *(16)*.

Overall, the results of band ligation are excellent, with long-term patient satisfaction greater than 90% *(12)*. In a large prospective study, 500 consecutive patients underwent rubber band ligation of internal hemorrhoids *(17)*, with successful results in 88% at 2-year follow-up. Symptomatic recurrence occurred in 12%. The high success rate, low incidence of serious complications, and ability to perform this inexpensive procedure in the outpatient settings make this technique the standard against which others have been compared.

Based on the safety and efficacy of rubber band ligation, novel methods to perform banding have been explored. A small study performed endoscopic hemorrhoid ligation using a flexible video endoscope with an attached band ligator *(18)*. Hemorrhoid size was reduced and resolution of bleeding occurred in 19 of 20 patients. Recently, new disposable, plastic, single-handed ligators have also been developed that employ suction to capture the hemorrhoidal tissue for band placement *(19,20)*.

Injection of sclerosing agents such as sodium morrhuate, absolute ethanol, or 5% phenol has been used in the treatment of first- and second-degree hemorrhoids. Using a sclerotherapy needle, sclerosant is injected into the surrounding submucosa at the base of the hemorrhoid. The ensuing inflammatory reaction produces fibrosis to fix the submucosa to the underlying muscle so prolapse cannot occur. Pain, mucosal sloughing, prostatitis, and infection can occur. Impotence has also been reported with sclerosant injection, presumably owing to damage to the cavernous plexus, which innervates the erectile tissue of the penis *(21)*.

Several other nonsurgical techniques are available for the management of internal hemorrhoids. Infrared photocoagulation is perhaps the most popular because of the low incidence of discomfort and other complications, but it is associated with a higher rate of retreatment because of recurrence compared with band ligation *(22)*. Laser techniques are efficacious but limited by cost constraints. Electrosurgical techniques have been applied to the treatment of internal hemorrhoids. Bipolar electrocoagulation has been found to be more efficacious and faster than direct current treatment *(23)*. Cryotherapy utilizes a special probe through which liquid nitrogen is applied to a hemorrhoidal cushion. Local tissue destruction is produced by freezing. Although cryotherapy can be used safely, it causes pain, relatively long healing times, and occasional stenosis or incontinence related to sphincter muscle damage. Compared with band ligation, patient satisfaction is less with more frequent local complications *(24)*.

Surgical therapy of internal hemorrhoids remains the most definitive means of treatment. Most patients can be managed with conservative techniques, and fewer than 10% require a surgical procedure *(25)*. Most third-degree, all fourth-degree, strangulated, and those hemorrhoids that have persisted despite other forms of therapy are best treated surgically. The surgical approach allows removal of all hemorrhoid tissue, excellent hemostasis, and rapid wound healing. The surgical approach is not without drawbacks including risk of infection, prolonged postoperative pain, urinary retention, and expense. Most surgeries can be performed

on an outpatient basis using local anesthesia. Multiple surgical strategies have been developed, but all are based on the principles of removing symptomatic diseased tissue, avoiding anal stenosis, and avoiding damage to the anal sphincter, which can lead to incontinence. Primary closure of the wound is often performed with excellent results and a low rate of wound infection *(26)*. However, some authors advocate closure of the rectal mucosa only to the dentate line, leaving the anoderm open to allow drainage. In a recent series, the open technique led to faster and more reliable wound healing with a similar rate of complications and incidence of pain *(27)*.

A metaanalysis of 18 available randomized, controlled trials assessing two or more treatment modalities for symptomatic hemorrhoids was performed to compare efficacy and adverse effects *(28)*. This analysis found that rubber band ligation was superior to sclerotherapy. In addition, patients undergoing rubber band ligation were less likely to require future therapy than patients being treated with sclerotherapy or infrared photocoagulation. Patients undergoing hemorrhoidectomy had a better response than those undergoing rubber band ligation. However, patients in the surgical group had a higher incidence of complications and significantly more pain. Based on these findings, it is reasonable to suggest rubber band ligation or a similar treatment as first-line treatment for grades 1–3 hemorrhoids, reserving hemorrhoidectomy for large grade 3 and grade 4 hemorrhoids and for patients who have failed other techniques.

Indications for Referral to a Specialist

Small carcinomas, anorectal varices, and rectal prolapse can be easily confused with hemorrhoids. Any unusual-appearing "hemorrhoid" warrants referral to an experienced surgeon to confirm the diagnosis. Although this may require only simple reinspection, endoscopy, biopsy, or examination under anesthesia may be necessary. Referral to a gastroenterologist or a surgeon is appropriate if pruritis, prolapse, or bleeding symptoms persist despite conservative therapy. Most grade 3 (prolapsing requiring manual reduction) and all grade 4 (irreducible) hemorrhoids require referral for an interventional or surgical approach. Severe pain associated with an acutely thrombosed external hemorrhoid may demand immediate surgical evacuation of clot. Any signs or symptoms of abscess or fistula associated with hemorrhoidal disease should prompt a surgical evaluation. Particular diligence is necessary in evaluating and treating hemorrhoidal disease in immunosuppressed patients and in those with inflammatory bowel disease or coagulopathies.

ANAL FISSURE

An anal fissure is a painful, linear, traumatic ulcer located in the anal canal, which extends from the margin of the anus to just below the dentate line. These small lesions can produce considerable pain and may be acute, recurrent, or chronic. Anal fissure is a common and sometimes misdiagnosed problem in both children and adults. One epidemiologic survey demonstrated that up to 10% of outpatients seen in proctologic clinics suffered from anal fissure *(29)*.

Pathophysiology

The initiating factor in the development of an anal fissure is trauma to the anal canal. Traditionally, the passage of a hard or large stool bolus was felt to be the precipitating event. However, a history of constipation preceding the onset of a fissure is seen in only approximately 25% of cases *(30)*. An important factor predisposing to anal fissure formation is high resting sphincter tone (primarily determined by the internal sphincter muscle). Maximal resting and voluntary contraction pressures are elevated in patients with anal fissure *(31)*. This explains the low frequency of anal fissures in the elderly, who typically have a relatively low sphincter tone, and also that virtually all therapy for fissure disease is directed at reducing resting anal sphincter pressure. More than 90% of anal fissures are located in the posterior midline. This is because the elliptical arrangement of the sphincters offers relatively less support to the posterior anal canal. This lack of muscular support predisposes this area to traumatic tears with passage of a large firm stool. A contributing factor, particularly in those with chronic anal fissure, is relative ischemia of the posterior anal canal. Studies have demonstrated decreased density of capillaries in the posterior midline portion of the internal sphincter and reduced blood flow at the posterior commissure of the anal canal in patients with fissures *(32)*. After sphincter pressure-reducing lateral internal sphincterotomy is performed in anal fissure patients, anodermal blood flow rises to levels seen in controls *(33)*.

Cardinal Signs and Symptoms

Sharp pain associated with scant, bright red rectal bleeding is the hallmark of anal fissure disease. The pain occurs during and after passage of stool "like passing a piece of glass." Pain may radiate into the rectum or buttocks and sometimes seems out of proportion to what would be expected given the small size of the lesion. If pain is severe enough, patients may have difficulty with urinary hesitancy, retention, or frequency. Anticipation of pain with bowel movements may discour-

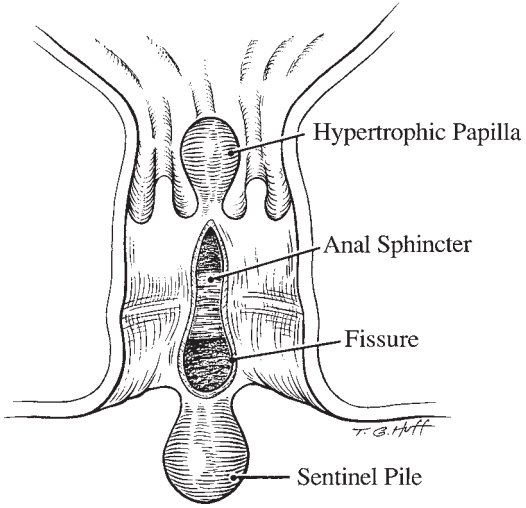

Fig. 2. The classic triad of chronic anal fissure: hypertrophic papilla, anal fissure, and sentinel pile. (Adapted with permission from ref. *2*.)

age subsequent stools. This sets up a vicious cycle of constipation, which only exacerbates the condition. Bleeding is generally self-limited and of low volume, spotting the toilet tissue or coating the stool surface. Repeated trauma at the site may cause intermittent bleeding. Patients may also develop discharge and pruritis.

Anal fissures are best identified by careful inspection. The buttocks should be aggressively spread with special attention to the posterior midline. Marked tenderness and sphincter spasm may limit the ability to perform a digital exam or anoscopy even with topical anesthesia, but such tenderness itself suggests a fissure, particularly in the absence of an acutely thrombosed hemorrhoid or other lesion. A fissure can be identified as a small, linear tear oriented perpendicular to the dentate line. Fissures are so commonly located in the posterior midline that, if found laterally, a predisposing disease process (such as inflammatory bowel disease, syphilis, tuberculosis, and others) should be considered. The classic triad of a chronic anal fissure includes (a) a sentinel pile or skin tag, the result of lymphatic edema and low-grade infection at the distal skin margin; (b) the fissure itself; and (c) a hypertrophied anal papilla proximally caused by edema and fibrosis (Fig. 2). An anal fissure must be differentiated from other perianal conditions that may have a similar presentation and appearance such as perirectal abscess, fistula-in-ano, perianal inflammatory bowel disease, thrombosed hemorrhoid, and squamous cell cancer of the anal skin.

Treatment

Acute anal fissures are approached with simple measures to avoid repeated trauma and allow healing. Stool bulking agents, adequate fluid intake, and stool softeners help break the cycle of hard stool, pain, and reflex spasm. Warm sitz baths relieve spasm and decrease resting anal canal pressure *(34)*. Topical anesthetics may provide temporary, symptomatic relief. However, in the treatment of acute anal fissure, the combination of dietary bran supplements and warm sitz baths was shown to be superior to a topical anesthetic or hydrocortisone cream with respect to symptoms and healing *(35)*. Most acute anal fissures will heal with a conservative regimen in 4–6 weeks.

Once fissures develop the features of chronicity, the likelihood of spontaneous healing is less than 50% *(36)*. Effective treatment for a chronic fissure centers on methods of reducing baseline sphincter tone. One such method is simply to apply topical nitroglycerin to the anus. Nitric oxide, a breakdown product of organic nitrates, meditates inhibitory neurotransmission of the internal anal sphincter *(37)*. Topically applied nitroglycerin allows healing of fissures both by reducing maximum resting pressure, producing a reversible "chemical sphincterotomy" *(38)*, and by increasing anodermal blood flow, which is important for fissure healing. Open trials and randomized controlled studies have demonstrated the efficacy of 0.2% nitroglycerin ointment therapy *(39,40)*. Although a controlled trial showed a 68% rate of healing at 8 weeks (vs. 8% for placebo), another recent large multicenter controlled study failed to confirm the efficacy of topical nitroglycerin *(41)*. Even with the typical application of only a tiny pea-sized dose twice daily, headache is a frequent complaint. Headache is a major problem using the 2% concentration available in this country, although pharmacies can specially compound the lower concentration. Recent uncontrolled studies have explored other smooth muscle relaxants such as bethanechol and diltiazem in an attempt to heal fissures without causing headaches. A recent controlled study of nearly 300 patients found excellent results (90% healing at 3 weeks) using nifedipine gel *(42)*.

Botulinum toxin inhibits calcium-dependent exocytosis of acetylcholine, producing muscle paralysis. Paralysis resolves once new axon terminals grow in the weakened muscle, typically 3–4 months later. Botulinum toxin, injected directly into the sphincter through the perianal skin, rendered most patients pain-free by 1 week and healed more than 80% of fissures by 3 months *(43,44)*. A randomized controlled trial proved 20 U of botulinum toxin to be superior to placebo in terms of symptoms and healing rate (73% vs. 13%) at 2 months *(45)*. Temporary

mild fecal incontinence appears to be rare. Botulinum toxin has been directly compared with 0.2% nitroglycerin ointment *(46)*. At 2 months, 96% of anal fissures were healed in the botulinum-treated group versus 60% in the nitroglycerin group.

Surgical sphincterotomy for chronic anal fissure remains the standard against which other therapies must be compared. The technique of choice is a lateral subcutaneous internal sphincterotomy, which lowers sphincter tone without the reported late "keyhole" deformity seen after posterior midline sphincterotomy. Cure rates of 90–95% may be expected, but damage to the sphincter is permanent, and long-term fecal incontinence occurs in approximately 8% of patients *(47)*. The American Society of Colon and Rectal Surgeons recommends caution before performing internal sphincterotomy in patients with diarrhea, irritable bowel syndrome, and diabetes and in the elderly *(48)*.

A recent randomized controlled trial compared topical nitroglycerin with surgical sphincterotomy and found the surgical procedure to be clearly more effective *(49)*. A reasonable but not yet evaluated strategy for chronic anal fissure disease may be to treat with a topical agent or botulinum toxin initially and to perform surgical sphincterotomy as "rescue" therapy in those who fail to respond.

Indications for Referral to a Specialist

Most acute and infrequently recurrent anal fissures should be treated conservatively but aggressively with sitz baths and stool bulking agents. Persistent symptoms or concern regarding the proper diagnosis requires referral to a specialist. Patients with chronic or frequently recurrent anal fissures that have failed to respond to conservative or topical therapy should be referred to an experienced surgeon or gastroenterologist for reexamination and consideration of botulinum toxin injection or sphincterotomy. The need for endoscopic examination or a careful anorectal examination under anesthesia may also prompt referral.

RADIATION PROCTOPATHY

The rectum, because of its fixed position in the pelvis and proximity to the prostate and uterus, is the most common GI site of radiation injury *(50,51)*. In a series of 738 patients with prostate cancer treated with radiation, proctitis of at least moderate severity was seen in 5% and anorectal stricture or fibrosis in 1% *(52)*. The incidence of severe proctitis was less than 1%, and most presented within 2–5 years after radiation exposure. Other studies have noted rates of proctitis of up to 20%. Acute radiation injury may develop during or shortly after radiation

treatment but usually resolves within 2–3 months. Chronic radiation injury is an ischemic process usually beginning 2–3 months after treatment has ended. Factors that may increase the likelihood of radiation injury include a history of lower abdominal surgery, concomitant medical illnesses predisposing to vascular disease such as diabetes or hypertension, and possibly chemotherapy *(53)*. Total radiation dose delivered and volume of tissue exposed also play a major role in the severity and incidence of complications *(54)*. Conformal radiotherapy techniques, which focus the high-dose volume of radiation to the affected tissue while sparing adjacent structures such as the rectum and bladder, produce fewer complications *(55)*.

Pathophysiology

The exact pathophysiology of radiation proctopathy is unclear. Acute injury has some similarities with inflammatory bowel disease, especially in the activation of mucosal cytokines *(56)*. Early tissue changes include mucosal cell loss, inflammation of the lamina propria, eosinophilic crypt abscesses, and endothelial swelling in the arterioles *(57,58)*. Although inflammatory changes are seen with acute radiation damage, chronic radiation "proctitis" is a misnomer because significant inflammation is absent, and the term proctopathy is preferred. Chronic radiation proctopathy is characterized by ischemic endarteritis, leading to submucosal fibrosis, serosal thickening, and vascular sclerosis *(59,60)*. This final common pathway is rectal tissue ischemia potentially producing mucosal friability, bleeding telangiectasias, ulcers, stricture, and fistulae *(53)*.

Cardinal Signs and Symptoms

Acute radiation injury produces symptoms of tenesmus, diarrhea, mucus production, and spotty bleeding. These nearly always resolve within days or weeks, and specific therapy is usually not necessary. Massive rectal bleeding, typically caused by a friable ulcer, may rarely occur as an early complication of radiation mucosal damage *(61)*. Chronic radiation proctopathy, although less frequent, is a more difficult problem. Complaints may include tenesmus, low-volume diarrhea, rectal pain, ulceration, and (rarely) even fistulous tracts into adjacent organs *(62)*. Hemorrhage is the most common feature of chronic radiation injury *(62)*. Bleeding, characteristic of a distal rectal source, is described as coloring the toilet tissue, coating the stool, or dripping into the toilet bowl. It ranges from an occasional mild spotting of little clinical concern to reddening of the toilet water with clots after every bowel movement, causing iron deficiency anemia or transfusion dependence *(63)*.

The diagnosis is best made by flexible sigmoidoscopy. Lesions typically begin near the dentate line and extend for a few centimeters proximally. The characteristic findings are pallor or patchy erythema of the mucosa with prominent telangiectasias, friability (easy bleeding with contact), and occasional ulcerations.

Treatment

Patients with intermittent minimal bleeding and normal red blood cell counts can be followed conservatively. In a study of 88 patients with radiation proctitis and mild to moderate symptoms, approximately one-half spontaneously became asymptomatic in 2 years *(60)*. However, none of the patients with severe symptoms and rectal ulcers stopped bleeding by 2 years. In a smaller series, but with longer follow-up, Cho et al. *(64)* observed 19 patients with radiation proctitis for a median of 12.8 years. Twelve became asymptomatic within 2 years without therapy.

Several medical therapies, which have modest benefits at best, have been attempted for patients who remain symptomatic. Aminosalicylic acid derivatives and/or corticosteroid enemas have not proved significantly useful in preventing progressive disease *(65,66)*. Sucralfate, an aluminum hydroxide complex of sulfated sucrose, has been used with modest success *(67,68)*. A controlled trial found sucralfate enemas to be superior to the combination of oral sulfasalazine and steroid enemas *(68)*. Misoprostil has shown some efficacy in reducing acute and chronic radiation symptoms in up to 36 weeks of follow-up following radiation therapy for prostate cancer *(69)*. Even hyperbaric oxygen therapy has been tried, with modest success in an uncontrolled trial *(70)*.

Short chain fatty acids delivered by enema have been used in the treatment of radiation proctopathy. Short chain fatty acids have multiple effects on the colon including differentiation and proliferation of colonic crypt epithelial cells *(71)* and are the preferred metabolic substrate for colonocytes. Small studies have demonstrated that short chain fatty acid enemas given twice daily for 4–5 weeks have produced mild clinical improvement and modest changes in bleeding *(72,73)*. A controlled, crossover trial failed to show significant benefit using butyric acid enemas *(74)*.

Topical treatment in the form of formalin therapy has been used for decades in the management of hemorrhagic cystitis associated with radiation injury *(75)*. The safety of formalin treatment has been demonstrated in both animal and human experiments, and it is free of systemic toxic effects when used with limited mucosal contact time *(76,77)*. For radiation proctopathy, a 4% formalin solution is infused into the

rectum or applied with soaked gauze pads. In one study, 22 of 29 patients who received one or two treatments with formalin had no more rectal bleeding, and 5 continued to have minor bleeding only *(78)*. Several other small studies have documented decreased bleeding and blood transfusion requirements with the use of intraluminal formalin treatment *(79,80)*.

Endoscopic cautery techniques are also highly effective in controlling radiation-induced rectal bleeding. Bipolar and heater probes are safe and effective in decreasing severe bleeding episodes, improving mean hematocrit values, and improving patients' impression of their overall health *(81)*. Lasers, including Nd:YAG, argon, and KTP have been used to cauterize the telangiectasias of radiation proctopathy successfully. Usually one to three sessions are required. The Nd:YAG laser, for example, has been shown to reduce the frequency of bleeding, increase the hematocrit level, and improve activities of daily living *(82)*. Argon plasma coagulation (APC) is a method of noncontact electrocoagulation in which high-frequency energy is delivered to the tissue through ionized argon. Thermal coagulation is typically to a depth of 2–3 mm, thus minimizing transmural necrosis, stricture formation, and perforation. APC has several advantages over laser, including a more superficial burn, portability, and cheaper cost *(83)*. APC treatment, like the other thermal modalities described, usually requires two to four treatment sessions and has been shown to be effective in decreasing symptomatic bleeding and increasing serum hematocrit *(84,85)*.

Patients with refractory symptoms who fail medical therapy have surgery as a possible final option. Reports from the surgical literature demonstrate that 8–18% of patients with radiation proctopathy eventually need surgery because of symptom intractability or local complications such as stenosis, perforation, or fistulae *(62)*. The chronic changes of radiation injury such as fibrosis, obliteration of tissue planes, and relatively ischemic tissue make surgical treatment of radiation complications hazardous *(86)*. Operations on the irradiated rectum have morbidity rates of 12–65% and mortality rates of 0–13%. The wide range reflects the diverse array of procedures used to treat the complications of radiation injury, which may or may not include primary anastamosis *(87,88)*. Surgical procedures, such as diversion, resection, or bypass, are primarily directed toward management of significant stenosis, fistulae, or refractory bleeding *(88)*. Because of the high complication rate, (a) surgery should be considered a last resort; (b) surgical procedures should be as simple and conservative as possible; and (c) there should be a high level of vigilance for such postoperative complications as wound infection, sepsis, obstruction, and fistulae *(89)*.

Indications for Referral to a Specialist

Referral for a flexible sigmoidoscopy is mandatory to evaluate hematochezia in confirming the diagnosis of radiation proctopathy and to rule out other sources of blood loss. Infrequent minor bleeding may be watched and oral iron therapy considered. Frequent, heavier bleeding or iron deficiency anemia is usually an indication for endoscopic therapy by a gastroenterologist experienced with thermal techniques. Surgical consultation may be necessary if symptoms persist despite aggressive endoscopic therapy or if complications such as fistula or stenosis develop.

MISCELLANEOUS CAUSES

Solitary Rectal Ulcer

Solitary rectal ulcer syndrome is a chronic benign disorder related to abnormal defecation. It is probably caused by mucosal trauma from straining, but direct digital trauma in an attempt to aid evacuation and possibly a primary neuromuscular pathology may also play a small role. Solitary rectal ulcer is stongly associated with internal intussusception of the rectal mucosa or overt rectal prolapse *(90,91)*. Prolapsing of rectal mucosa combined with high transmural pressures during defecation may be responsible for the mucosal trauma that causes ulceration *(92)*. Characteristic histologic findings are extension of muscularis mucosa between crypts, muscularis propria "disorganization," fibrous obliteration of lamina propria, and regenerative changes in crypt epithelium *(93)*.

Solitary rectal ulcer syndrome typically presents in a patient with a history of constipation, incomplete evacuation, and chronic straining at stool who may also use digital maneuvers to empty the rectum *(94)*. Rectal bleeding and associated mucus passage is usually scanty with coating of the stool or tissue. Severe bleeding is rare *(95)*. The diagnosis is made by endoscopy, by which classically, a shallow, discrete, 1-cm punched-out ulcer with a hyperemic margin 7–10 cm from the anal verge on the anterior rectal wall is identified. The term "solitary rectal ulcer" is somewhat of a misnomer, however, because endoscopic examination may show several small clustered ulcers or may reveal no ulcer at all. Instead, a localized hyperemic patch of tissue or a polypoid mass initially suggestive of a malignancy may be appreciated.

Treatment is primarily aimed at improving defecation habits. The combination of education, the liberal use of fiber and/or laxatives, and bowel habit retraining has enjoyed some success *(96,97)*. Topical agents

such as steroids and 5-aminosalicylic acid enemas have not been proved effective *(94,98)*, although sucralfate enemas may be *(99)*. Biofeedback has been shown to decrease bleeding by producing less straining and may also decrease postsurgical symptomatic recurrences *(100,101)*. Symptoms that continue and are refractory to conservative measures may respond to surgical rectopexy to "tack up" the internally prolapsing mucosa *(102)*.

Anorectal Varices

Anorectal varices are a result of portal hypertension and represent enlarged portal-systemic collaterals. They develop as a result of hepatofugal portal venous flow through the inferior mesenteric vein to the superior hemorrhoidal veins. An important distinction is that anorectal varices are not related to hemorrhoids, which are vascular cushions of ectatic venular-arteriolar connections of the hemorrhoidal plexus, and have no direct connection to the portal system. The prevalence of anorectal varices varies somewhat, ranging from 43 to 78% in patients with cirrhosis *(103–105)*. Anorectal varices are usually discrete, serpentine, submucosal veins. In contrast to external hemorrhoids, varices are compressible and refill rapidly. They extend from the squamous portion of the anal canal and cross the dentate line into the rectum proper. Distinguishing hemorrhoids from varices is important because of the risk of severe, recurrent hemorrhage with varices and the different approach to therapy.

Bleeding from anorectal varices is relatively uncommon, with an incidence between 1 and 8% *(103,106)*. The severity of this bleeding varices from occult, insidious bleeding to massive, life-threatening, or even fatal hemorrhage *(104,107)*. Various measures have been attempted to control hemorrhage associated with anorectal varices. Therapeutic failures have been reported for rectal tamponade *(108)* and vasopressin infusions *(109)*. Endoscopic therapies, including band ligation and sclerotherapy, have been used, but not always successfully, and sometimes with fatal outcomes *(110,111)*. Surgical suturing of the variceal columns prevents hemorrhage in most cases with relatively low morbidity. Anorectal varices seem to rebleed in most patients unless a definite reduction of portal venous pressure is achieved. The transjugular intrahepatic portosystemic shunt has emerged as an effective means of reducing portal pressure in order to control bleeding caused by anorectal varices *(112,113)* and may become the definitive therapy in the future.

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12 Obscure Causes of Acute Lower Gastrointestinal Bleeding

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CONTENTS

INTRODUCTION

In contrast to chronic or occult bleeding, acute lower gastrointestinal (GI) bleeding can be a confusing conundrum and a diagnostic dilemma. The difficulty is exacerbated by the severity and rapidity of the clinical problem, since by definition it involves instability of vital signs, anemia, and/or the need for blood transfusion *(1)*. Unfortunately, the diagnostic and therapeutic approach to the patient with severe lower GI bleeding has not been well standardized. The clinician cannot rely on generally accepted guidelines, since there is a paucity of evidence-based recommendations. This uncertainty is an unavoidable fact that can be uncomfortable for the primary care physician and anxious patients or family who have unrealistic expectations that definitive diagnosis and treatment may be possible even in this situation. Many patients with unrevealing colonoscopy, radiology, and nuclear medicine scans are simply transfused, with the hope that their bleeding will stop spontaneously and not recur after discharge. Unfortunately, in about 20% of patients, bleeding recurs or continues. In many cases an empiric

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resection of some or the entire colon is done, but the mortality is high in these typically elderly patients. Many who survive such surgery continue bleeding, especially if only a partial resection is performed.

Clinical Challenges

The clinical challenges in treating lower GI bleeding include the following:

- Elusive and obscure etiologies including an extensive differential diagnosis.
- The fact that lesions may be subtle, unfamiliar, or virtually impossible to detect because they have minimal mucosal abnormalities or extension.
- The possibility that no lower GI source actually exists. In as many as 11% of patients suspected initially to have lower GI bleeding, an upper GI source is ultimately found *(2)*. Although the presence of frank blood from a nasogastric aspirate confirms an upper GI bleed, a negative aspirate does not rule this out. However, the presence of bile without blood makes an upper source unlikely *(3)*.
- Uncertainty about which of several lesions found are the source(s) of bleeding.
- Unavailability of adequate methods to diagnose some obscure sources of lower GI and small intestinal bleeding beyond the reach of standard endoscopic instruments.
- Lower GI bleeding is generally more difficult to evaluate clinically than upper GI bleeding. Endoscopy of the unprepared colon is more difficult than upper endoscopy, and lesions may be missed in a dirty colon because of poor preparation or active bleeding *(4)*. Conversely, the diagnostic ability of other tests requires active flow at the bleeding site at the time of examination, because of an extremely variable range of bleeding rates with very intermittent timing of bleeding.
- Lack of development of reliable algorithms to guide management, because of insufficient evidence for this disorder based on randomized prospective clinical trials.

Epidemiology

The annual incidence of lower GI bleeding is much less (20.5–27 cases per 100,000 adult population at risk) and generally has a less severe course than upper GI bleeding (100–200 cases per 100,000). Age is the strongest risk factor for lower GI bleeding, with an approximately 200-fold increase in the elderly compared with young adults. This rise in incidence most likely represents the increasing prevalence of colonic diverticulosis and colonic angiodysplasia with age. The mean age of patients with lower GI bleeding ranges from 63 to 77 years, and

the reported mortality rate is 2–4%. As for upper GI bleeding, lower GI bleeding stops spontaneously in most cases (80–85%).

DIAGNOSTIC APPROACH

After initial evaluation and volume resuscitation, further management depends on the results of a nasogastric tube aspirate. About 1000 mL or more of blood is required to cause hematochezia from an upper source, and hemodynamic compromise is typically an accompanying feature. If copious nonbloody bile is seen on nasogastric aspiration, the physician should proceed directly to a colonoscopy. In all other cases, however, the colonoscopy should be preceded by an esophagoduodenoscopy (EGD), because in as many as 10–15% of patients with suspected lower GI bleeding, the source is the upper GI tract. The diagnostic yield from colonoscopy ranges from 60 to 80%. Timing of colonoscopy with or without upper endoscopy has not been systematically studied, but it should be performed as soon as possible in patients with continuous hematochezia. Patients who have stopped bleeding can undergo examination on a semielective basis.

History and Physical Examination

The focus initially should be to establish the quantity and color of blood and elicit any symptoms of hemodynamic instability that would require immediate intervention. The medical history can then evaluate previous GI bleeding episodes and diagnoses associated with recurrent episodes of bleeding. These include diverticulosis, angiodysplasias, hemorrhoids, ulcers, varices, or inflammatory bowel disease. Other important history findings include comorbid diseases, coagulopathies, liver disease, nonsteroidal antiinflammatory drug use (NSAID), and radiation therapy affecting the abdomen or rectum (prostate). NSAID use is a very important risk factor, now recognized as the cause of not only upper GI bleeding, but also increased lower GI bleeding.

Laboratory Tests

Obviously, no laboratory test can be diagnostic for a lower GI source of bleeding. An elevated BUN-to-creatinine ratio is suggestive of upper GI hemorrhage, particularly when above 33–36, but below this level it is not helpful in determining the source.

Although initially in acute bleeding they may not decline until fluid is given for resuscitation, the hemoglobin and hematocrit are important for evaluating all patients, except those who are young, stable, and without significant bleeding. The hemoglobin decreases to less than 10 g/dL

in about one-third of patients with lower GI bleeding, compared with two-thirds of those with upper GI bleeding. Some admitted patients may need blood typing, and all patients becoming unstable should be blood typed and crossed for 2–6 U. Beyond these recommendations, the condition and clinical assessment of the patient determine the need for further testing and the frequency of monitoring.

Anoscopy or Sigmoidoscopy

These examinations may be a useful early test in patients with presumed lower GI bleeding to exclude obvious distal lesions such as bleeding hemorrhoids, anal fissure, rectal ulcer, proctitis, or rectal cancer. These procedure may not reveal the source if done while bleeding is still brisk, because it is often impossible to tell whether blood is coming from above the scope or from a lesion at or below the examined level. Sigmoidoscopy is usually reserved primarily for younger patients (<40 years old) with relatively minor bleeding.

Barium Enema

Contrast studies of the colon should not be relied on for the initial diagnosis of ongoing lower GI bleeding *(5,6)*. Barium enema has many disadvantages, for the following reasons:

- It cannot detect vascular anomalies, a very frequent cause of lower GI bleeding.
- Good visualization of diverticula (common in the elderly) is not sufficient evidence that diverticula are the only cause of the apparent lower GI bleeding.
- It may fail to diagnose the presence of a malignant lesion and has a miss rate five times that of colonoscopy. It diagnoses 85% of cancers versus 97% for colonoscopy.
- Even if a suspicious lesion is seen, colonoscopy is usually required for definitive diagnosis (to obtain biopsies) and possible treatment, regardless of barium enema findings.

Although a double-contrast barium enema several days after the bleeding ceases may be a helpful procedure, colonoscopy is still the preferred diagnostic procedure, because it is frequently required regardless of the results of a barium enema study. Moreover, it is important to keep in mind that a colon full of barium interferes with subsequent colonoscopy or arteriography.

Colonoscopy

Colonoscopy has gained widespread support during the past few decades for the early and rapid diagnosis and treatment of many cases

of lower GI bleeding. Unless an obstructing colonic lesion or pending perforation from ischemia or another cause is suspected, preparation for urgent colonoscopy should include a rapid oral purge, using a large volume (4–8 L) of lavage solution after the acute bleeding has stopped *(1)*. Bowel preparation can usually be accomplished within about 4–6 hours after admission, to be promptly followed by colonoscopy. However, its use in severe or massive continuing lower GI bleeding is still controversial. In one report, colonoscopy during active bleeding did carry a greater risk in comparison with routinely scheduled colonoscopy, required more "experience and skill" from the endoscopist, and was more difficult. In such cases, intubation of the terminal ileum at the time of colonoscopy may be useful, particularly when there is blood throughout the colon, as fresh blood emanating from the ileum is indicative of small intestinal bleeding.

Adequate purge preparation prior to colonoscopy facilitates a more thorough examination and does not increase the likelihood of rebleeding. Complications such as perforation are actually more common in the uncleansed colon owing to the poor visibility *(2)*. The overall diagnostic yield is 69–80% if the bowel has been cleansed adequately for good visualization *(2,7,8)*. Several large clinical series report that the most common findings in lower GI bleeding are diverticula (judged to be causal in a maximum of about 40% of patients) and vascular ectasias (30%) *(9,10)*. Colitis caused by radiation or ischemic or inflammatory causes is found in about 20%, colonic neoplasia in 14%, and anorectal causes in 10%. If identified, the source of bleeding should be treated appropriately. Colonoscopy can have both a diagnostic and therapeutic role in the management of angiodysplasia, radiation colitis, or polypectomy sites and occasionally can be successful in treating a bleeding diverticulum.

Small Bowel Imaging by Enteroclysis, Enteroscopy, or Given Capsule

When the bleeding site remains obscure or undetermined after thorough upper and lower endoscopy, the evaluation should focus on the small bowel and right colon, where most obscure cases of bleeding occur. Obscure GI bleeding, especially when severe or refractory, is best managed by a team approach including the primary care physician, radiologist, intensivist, gastroenterologist, and surgeon.

Enteroclysis is preferred to standard barium small bowel follow-through series because of greater sensitivity. The technique is available in most radiology departments and requires intubation of the small bowel to the duodenojejunal junction, with controlled infusion of barium,

methylcellulose, and water to achieve a double-contrast effect. The sensitivity of barium studies is poor for many causes of bleeding and cannot detect angiodysplasias.

Enteroscopy is available primarily at tertiary care centers, requires considerable endoscopic expertise, and has only a moderate sensitivity. Small bowel bleeding may be difficult to diagnose by even the longest enteroscopes, since looping prevents scope passage far beyond the ligament of Treitz in most cases. Complete endoscopic examination and treatment of the intestine is possible only when done intraoperatively, when the intestine can be manually advanced over the scope by a surgeon assisting the endoscopist.

Capsule endoscopy is a major recent advance that provides good visualization of the entire small intestine. Images are obtained by a capsule (13-mm diameter) that is swallowed and propelled by normal peristalsis within a few hours through the entire GI tract, with images taken many times per minute and sent by radio to a recording device that is worn on a harness around the patient's abdomen. The images can be reviewed at high speed after the study is completed. Angiodysplasias can be easily detected in a significant proportion of patients by capsule endoscopy. Although it is less invasive, a major limitation compared with intraoperative endoscopy is that capsule endoscopy does not allow any immediate therapeutic interventions. The Given capsule should not be used in patients suspected to have tight intestinal strictures (such as in some patients with Crohn's disease), because of the risk of obstruction. It is not very useful for evaluating the colon, because the capsule does not remain oriented longitudinally and tumbles, so images are not obtained of the entire surface as is the case in the small intestine.

Radionuclide Scans

Nuclear bleeding scans using either 99m Tc sulfur colloid or 99m Tc-labeled erythrocytes have the advantage of being noninvasive, and easy to perform and requiring no patient preparation *(11,12)*. Diagnosis of active bleeding by either method requires several criteria: (a) that the tracer extravasate locally into the lumen of the intestine; (b) that increases in intensity occur over time; (c) that bleeding conform to the anatomy of the small or large intestine; and (d) that the bleeding move within the lumen by antegrade or retrograde peristalsis.

99m Tc-sulfur colloid tracer is cleared by the liver and spleen, so bleeding sites in the upper abdomen may not be visible amid the heavy tracer accumulation in these organs. Imaging using this particular form of tracer can be done only for a very limited time interval because its circulating half-life is 2–3 minutes. After 20 minutes, essentially no

tracer remains in the bloodstream. Thus, hemorrhage goes undetected unless active bleeding occurs within about 10 minutes after injection.

Intermittent bleeding can be detected better by labeling red blood cells in vitro with 99m Tc; after reinjection into the patient, they act as a blood pool scan. 99m Tc-labeled erythrocyte activity remains in the bloodstream for 24 hours. Patients are often imaged continuously for 1–2 hours initially, significantly increasing the likelihood of detecting intermittent bleeding. If the scan is initially negative, the patient can be rescanned without reinjection later, as clinically indicated, for 24 hours *(13)*. The benefit of this approach is that the abdomen can be scanned over a prolonged period to permit accumulation of enough isotope to be detected by the γ-counter in the case of moderate bleeding and to detect intermittent bleeding. Because of these advantages, most hospitals prefer 99m Tc-labeled erythrocytes to evaluate lower GI bleeding *(14)*. Some authors have suggested that 99m Tc-labeled erythrocytes are nearly as sensitive as 99m Tc-sulfur colloid and can detect bleeding rates as slow as 0.1 mL/min.

Extreme caution should be used in interpreting radionuclide scans. It is important to recognize that bleeding scans may be normal in up to 70% of patients later documented to have a lower GI source of bleeding. On the other hand, a positive scan may identify the wrong area in as many as 30–50% of bleeding colonic lesions. Another limitation is that localization of the site of bleeding is somewhat indefinite because of movement of extravasated contrast material by bowel peristalsis. Depending on the time between images, it may be impossible to tell exactly where in the GI tract the radionuclide entered. Radionuclide scans may be useful if they provide a clue to the most likely source of bleeding for subsequent angiography, colonoscopy, or surgical therapy.

Angiography

There are two situations in which diagnostic angiography are helpful. First, in the patient who is bleeding massively, angiography can detect the site of bleeding (i.e., right or left colon, small bowel, upper GI tract) and, in some instances, determine whether the lesion is a diverticulum, a vascular anomaly, or a tumor. Beyond directing the surgeon to the correct location, selective angiography permits either infusion of vasopressin or embolization directly into the bleeding artery.

Because patients with negative radionuclide scans may have positive arteriograms, and lesions may be identified by angiography even in the absence of extravasation, some would consider it reasonable to obtain an arteriogram without delay in patients with major lower GI bleeding in whom colonoscopy is unrevealing or cannot be performed.

A major limitation of diagnostic and therapeutic angiography is the risk of renal failure from intravenous contrast material.

The overall yield of angiography is 40–78% *(15)*. Diverticular disease and angiodysplasia are the most common findings *(15–18)*. Other lesions include peptic ulcer, Meckel's diverticulum, neoplasm, and vascular-enteric fistula. Angiography may also define lesions with abnormal vasculature, such as vascular malformations or tumors, even if extravasation of contrast material is not noted. This is useful in patients with acute massive bleeding that has slowed by the time of angiography or in patients with chronic or recurrent bleeding in whom a diagnosis has been difficult to establish. A bleeding rate of 1 mL/min during angiography is generally required for a positive result, much higher than that needed for scintigraphy (as low as 0.1 mL/min) *(19,20)*, although rates as low as 0.4 mL/min have been detected.

MRI or Helical CT Scans

Some new variants of computed tomography (CT) and magnetic resonance imaging (MRI) techniques are under investigation that may be useful for the diagnosis of GI bleeding. MRI after administration of an intravascular contrast agent may be capable of detecting and localizing GI hemorrhage of the colon *(22)*. CT angiography is a method of rapid helical CT scanning after intraarterial injection of contrast media that has been reported to improve the detection of arterial sources of GI bleeding *(23)*.

SPECIFIC CAUSES OF OBSCURE LOWER GI BLEEDING

Vascular Diseases

Angiodysplasia (Submucosal Vascular Ectasia) and Arteriovenous Malformations

Angiodysplasia are responsible for 3–12% of cases of acute lower intestinal bleeding. They are acquired lesions of aging that occur equally in men and women and are thought to result from dilation and tortuosity of the submucosal vessels owing to increased colonic intraluminal pressure *(24–26)*. Most are located in the cecum and proximal ascending colon *(26)*. These mucosal lesions are not visualized by barium enema. Colonoscopy demonstrates a red flat lesion, about 2–10 mm in diameter. Instrumental artifact (small mucosal hemorrhages induced by scope suction) may appear similar but can be distinguished from angiodysplasias because the latter have an irregular margin resulting from its connection to the adjacent capillary bed, whereas the suction artifacts usually have a smooth margin. Colonoscopy is the most sensitive and

specific diagnostic technique. Angiodysplasia may be missed at colonoscopy because of the small lesion size or hypotension, which decreases angiodysplasia perfusion; they are more often missed because the mucosal lesion is covered by stool or blood clots in an inadequately prepared colon *(27,28)*. Most patients with an episode of bleeding from angiodysplasia require no treatment because bleeding stops spontaneously.

Angiodysplasia can be treated by colonoscopic electrocoagulation *(29)*. Because rapid bleeding may obscure the field when electrocautery is incomplete, large angiodysplasia should be treated around the circumference initially to obliterate peripheral vessels before treating the central target lesion. Because there is a higher risk of perforation from electrocautery for angiodysplasia in the right colon than in the left colon, the use of low power settings in the right colon is recommended. Angiography may also detect angiodysplasias and can treat them by embolotherapy. Other lesions must be excluded by colonoscopy before a right hemicolectomy for persistent or recurrent bleeding from angiodysplasia is performed.

Vasculitis

Systemic vasculitis (polyarteritis nodosa, systemic lupus erythematosis, dermatomyositis, Henoch-Schönlein purpura) may affect multiple organs, including the GI tract *(30–32)*. The most common presentation with GI involvement is ischemic bowel disease and perforation, but significant bleeding occurs in some cases. Colonoscopy in these patients may detect multiple petechial or ecchymotic lesions, and biopsies are compatible with evidence of vasculitis.

Aortointestinal Fistula

This disorder usually involves a small connection into the third portion of the duodenum where it crosses the aorta, particularly when the patient has a history of prior surgery for an aneurysm with Dacron graft placement or mycotic aneurysms, but it can occur (rarely) in patients with atherosclerosis. Very rarely, similar fistulae may rupture into the jejunum, ileum, or colon. A "herald" bleed may precede massive exsanguinating hemorrhage. To save the life of these patients, a very high index of suspicion is necessary to make the diagnosis because endoscopic examination may reveal no visible lesions or only a small clot. Arteriography or CT scan may demonstrate evidence of the fistula, but surgery should not be delayed while one awaits radiologic confirmation if the diagnosis is suspected based on the history of a Dacron aortic graft and there is massive bleeding.

Intestinal Varices

Intestinal varices are rare but may present with massive bleeding. This unusual cause of lower GI bleeding in patients with portal hypertension can be identified on the venous phase of a superior mesenteric angiogram, or by Doppler ultrasound. Treatment is decompression of the portal hypertension by medications such as propranolol or octreotide, interventional radiology with transjugular intrahepatic portosystemic shunt (TIPS), or surgery. Ileal or colonic varices have a predilection for developing around ostomies *(33,34)*. Portal colopathy is a condition of multiple colonic vascular ectasias in patients with portal hypertension *(35)*. Severe bleeding from rectal varices may also occur in these patients.

Diverticula

Diverticulosis of the Colon

Colonic diverticula are thought to be the most frequent cause of lower intestinal hemorrhage in the elderly, but the precise percentage is uncertain for several reasons. First, diverticula are very common in the general population older than age 50, with a prevalence increasing linearly with age and affecting most people by age 80. Second, proof of bleeding from any diverticulum is very difficult to establish by angiography or colonoscopy because the bleeding episodes last a very short time and are intermittent, and pathologic examination of resected colons in these patients does not often reveal evidence of arterial rupture into a diverticulum. Thus, the diagnosis is usually based simply on the presence of diverticulosis and the failure to identify other definite causes *(36)*.

Although most diverticula are located in the descending and sigmoid colon, most angiographically proven diverticular bleeding arises from the proximal colon. By contrast, in about 60% of patients with colonoscopically diagnosed diverticular bleeding, diverticula are found in the sigmoid or left colon. These data imply that more serious diverticular bleeding tends to be from the right colon.

A conservative approach to therapy is recommended, because bleeding from diverticula ceases spontaneously in 80% of cases. Once bleeding has stopped, colonoscopy can be done after thorough lavage preparation to exclude other causes. Surgery for recurrent bleeding can then be considered but should be avoided in the elderly patient when possible. Because most diverticula do not bleed repeatedly, patients with an episode of resolved lower GI bleeding originating from a diverticulum can usually be discharged without surgery.

Meckel's Diverticulum

Meckel's diverticulum is the most common congenital GI anomaly. This anomaly represents persistence of the omphalomesenteric duct. Bleeding can occur because of ulceration of ectopic oxyntic gastric mucosa that in some cases lines the diverticulum *(37)*. 99m Tc pertechnetate is taken up by the ectopic gastric mucosa present in most Meckel's diverticula that bleed. Thus, nuclear medicine imaging with 99m Tc pertechnetate is the method of choice that should be used early in the evaluation of young patients with lower GI bleeding. This technique is approximately 90% accurate *(38)*. The lesion is treated by surgical excision.

Colitis

Infectious Colitis

Acute onset of bloody diarrhea associated with crampy abdominal pain and fever should suggest the possibility of an infectious colitis caused by bacterial pathogens such as *Shigella*, *Campylobacter*, *Salmonella*, or toxigenic *Escherichia coli* O157:H7 or by amoebic dysentery. Lower intestinal bleeding caused by pseudomembranous colitis owing to *Clostridium difficile* infection is very uncommon and generally not severe. These colonic infections do produce acute inflammatory changes that can be detected by colonoscopy or sigmoidoscopy. Accurate diagnosis can be difficult before results of stool cultures become available. Antibiotics are highly effective for treatment of shigellosis and amebiasis but are ineffective or minimally effective against salmonellosis, *Campylobacter* infection, and enterohemorrhagic *E. coli* infection. Fortunately, the latter two generally resolve spontaneously without sequelae.

Ischemic Colitis

Ischemic colitis causes about 3–9% of cases of acute lower intestinal bleeding *(36,39)*. The usual presentation is sudden onset of lower abdominal pain followed by moderate hematochezia, but occasionally bleeding is more severe. The greater frequency of ischemic colitis in the elderly suggests a relationship to degenerative changes in the vasculature. However, angiography plays little role in the evaluation because it rarely demonstrates significant abnormalities, and some atheromatous changes that are almost universal in the mesenteric circulation of the elderly are of uncertain pathogenic significance in ischemic colitis. Ischemic colitis is much more common, but it should be differentiated from the rarer but potentially more lethal acute mesenteric ischemia. Patients with acute mesenteric ischemia appear sicker, have more severe

abdominal pain, and usually have an acute precipitating event. Angiography is useful in mesenteric ischemia. In contrast, vascular occlusion or any obvious precipitating event usually cannot be identified in ischemic colitis. Patients suspected of having colonic ischemia should undergo gentle colonoscopy or barium enema as the initial diagnostic test. Ulcerative lesions associated with area of edema and pallor at colonoscopy are suggestive of ischemia. Biopsy shows necrosis, in contrast to the findings seen in ulcerative colitis. Most cases of colonic ischemia resolve spontaneously within days to several weeks.

Radiation Proctitis and Colitis

Approximately 3% of lower GI bleeding, particularly among the elderly, is caused by radiation proctitis or colitis. The onset of bleeding is usually 1–4 years after irradiation, when telangiectasias develop as a consequence of arteriolar injury in the field irradiated. A history of irradiation for prostate cancer in men, or cervical or other gynecologic cancer in women, strongly suggests that radiation proctitis or colitis is the cause of lower GI bleeding. Sigmoidoscopy or colonoscopy is diagnostic, and laser therapy or argon plasma coagulation of the telangiectasias are effective treatments for bleeding.

Inflammatory Bowel Disease (Ulcerative Colitis or Crohn's Disease)

Although some bleeding is a common manifestation of inflammatory bowel disease, acute major lower GI hemorrhage is relatively rare, representing only 0.1% of all admissions for ulcerative colitis and 1.2% for Crohn's disease in a 7-year series at the Mayo Clinic *(40)*. Lesions are often seen on colonoscopy, but most of these cannot be treated endoscopically. Surgery is required in less than half of cases during the initial hospitalization. Recurrent hemorrhage is not rare, and for these cases surgery may be the most appropriate treatment.

Neoplasms (Adenomas, Carcinomas, and Other Tumors)

Benign or malignant neoplasms most often present initially with intermittent or only trace or minor amounts of bleeding, but in about 10% of patients significant bleeding may develop. The treatment for benign adenomatous polyps of the colon is usually snare polypectomy; treatment for carcinomas is surgical resection. Recurrent bleeding may occur soon after colonoscopic polypectomy if the polyp was resected before enough cautery could be applied for adequate hemostasis of the blood vessel in the stalk. Postpolypectomy bleeding has decreased from 2–3% previously to 0.2–0.6% recently, as there has been increasing use of blended electrocautery current in the polypectomy snare. Delayed

bleeding may occur 2 or more weeks or longer after polypectomy, possibly from sloughing of the clot *(41)*. Early postpolypectomy rebleeding can be managed by resnaring the stalk and applying pressure without electrocautery. Delayed bleeding can be managed in most cases conservatively by observation alone, providing blood transfusions if needed. When bleeding is severe or persistent, colonoscopic therapy may include injection of epinephrine or other agents, electrocautery, or endoscopic ligation with rubber bands or placement of metallic clips.

Mechanical Abnormalities (Volvulus, Intussusception, and Incarcerated Hernia)

Mechanical problems that cause an interruption in the blood supply to the intestine lead to mucosal injury and eventual bleeding from the area of ischemic damage, as discussed above in the Ischemic Colitis section. Volvulus or intussusception both cause a segmental strangulation of the small bowel that can be associated with the passage of "currant jelly" stools, a combination of mucus and blood. They both may present with crampy abdominal pain initially, followed by bloody stools. These diagnoses are often suggested by the findings on plain abdominal X-rays or barium studies. Except in the case of sigmoid or cecal volvulus that can be decompressed by colonoscopy, emergent surgery is needed for intestinal volvulus because of the risk of perforation.

In intussusception, typically a polyp or malignancy is the main cause. This disorder is more common in children, who may have therapeutic reduction on barium enema followed by colonoscopic polypectomy if benign polyps are found after the colon can be completely cleansed. Treatment of intussusception in adults is usually surgical, since malignant tumors are more likely. Incarcerated hernia can also present with blood owing to ischemic injury and is treated surgically.

Other Obscure Etiologies

Dieulafoy's lesions are minute mucosal defects that may be barely visible on endoscopy but can bleed significantly because they are located directly over a submucosal artery. These lesions were long ago recognized as a cause of upper GI bleeding but more recently were reported as a cause of obscure lower GI bleeding from the intestine or colon *(42)*. Elastic tissue disorders such as pseudoxanthoma elasticum and Ehlers-Danlos syndrome are rare hereditary diseases that can be complicated by lower GI bleeding *(43,44)*. Other disorders that can be recognized by their manifestations in the skin include the Osler-Weber-Rendu syndrome of hereditary hemorrhagic telangiectasia and the blue rubber bleb nevus syndrome *(45)*. The lesions are visible endoscopically. Bleeding

sources may be treated by methods such as bicap electrocautery, laser, or argon plasma coagulation. Because the lesions are located throughout the GI tract, it is often impossible to ablate them all.

NSAID-Induced Lower GI Bleeding

With the advent of the selective cyclooxygenase-2 (COX-2) inhibitors, drugs are available that provide an alternative to the higher risk of bleeding and GI ulcers caused by NSAIDs. Recently awareness has increased that NSAIDs cause not only upper GI bleeding but also a generalized enteropathy affecting the small intestine and colon. Bjarnason et al. *(46)* found that colonic ulcers and bleeding that may be life-threatening can be caused by NSAIDs. These drugs also cause an NSAID colitis and exacerbate classic inflammatory bowel disease. Wilcox et al. *(47)* found that most patients with lower GI bleeding are NSAID users (odds ratio, 2.6 increased risk). Several studies support a temporal and pathogenic relationship between NSAID use and lower intestinal bleeding. In one study of documented diverticular bleeding, 92% of patients had been taking NSAIDs. Patients with diverticular bleeding were more likely than those not bleeding to be taking a combination of NSAIDs and aspirin, and patients who rebled generally had resumed taking NSAIDs *(46–48)*.

TREATMENT

Endoscopic Therapy

The American Society for Gastrointestinal Endoscopy has provided guidelines for the management of lower GI bleeding *(49)*. These guidelines state that "the first priority is to stabilize the patient with intravenous fluids and transfusions if necessary. The diagnostic evaluation can begin while these resuscitative efforts are under way or as soon as the patient is stable, depending on the urgency of the situation. The colon is cleansed, preferably by lavage with 3–4 L of electrolyte solution given orally or through a nasogastric tube. The delay required for preparation is rarely a significant disadvantage since other resuscitative measures may be carried out at the same time, and only rare patients bleed so rapidly that a delay of a few hours jeopardizes hemodynamic stability."

Colonoscopy can identify a bleeding lesion in 50–70% of patients examined and has the advantage that definitive treatment is possible during the emergent or subsequent elective colonoscopic procedure. Methods of treatment include fulguration with electrocautery, snare cautery, heater probe, injection therapy, argon plasma coagulation, or laser photocoagulation.

Diverticular Hemorrhage

When diverticulosis is the cause of lower GI bleeding, it is not usually possible to identify a visible vessel or clot within a particular source diverticulum at the time of colonoscopy, but finding these lesions is useful because it may denote those patients at high risk for persistent or recurrent diverticular bleeding *(50)*. Pathologic examination of resected specimens may show erosion of an artery into either the dome or the orifice of the diverticulum. The lesion, if seen, can be treated by the usual methods: bipolar/multipolar electrocautery, heater probe, or epinephrine injection, independently or together, for control of bleeding. Endoscopic placement of metallic clips can also provide hemostasis *(51)*. Colonoscopic treatment may prevent recurrent bleeding and reduce the need for hemicolectomy *(52)*. Massive diverticular bleeding may not be amenable to endoscopic therapy because of poor visualization of the colon. Radiographic or surgical therapy should be considered for persistent or recurrent hemorrhage, but most cases stop bleeding with conservative management.

Angiodysplasia

Colonoscopic therapy for angiodysplasia is widely accepted and frequently successful. These lesions are also known as vascular ectasias or arteriovenous malformations and are acquired lesions most often found in the cecum and right colon. Treatment is successful in about 90% of cases using thermal cautery to coagulate and obliterate the vessels in the lesion *(53)*. Lower power settings than those used for bleeding gastroduodenal ulcers may be recommended owing to the increased risk of perforation in the right colon *(29,54)*. The periphery of the lesion should be treated before the center to obliterate the surrounding feeder vessels.

Radiation Colitis

Bleeding from multiple telangiectatic lesions in the distal colon produced by radiation therapy for prostate or gynecologic cancers (radiation proctitis or colitis) can be effectively treated with thermal contact probes, laser therapy, or newer noncontact modalities such as the argon plasma coagulator.

Polypectomy Site Bleeding

Postpolypectomy bleeding may occur immediately or weeks after the procedure. As for most other causes of lower GI bleeding, most polypectomy sites will stop bleeding spontaneously *(55,56)*. A number of methods are available to treat persistent bleeding, including electrocautery

with or without epinephrine injection, endoscopic band ligation of the polypectomy site, metallic clip placement, and the argon plasma coagulator. Surgical or radiologic intervention is only rarely necessary.

Hemorrhoidal Bleeding

Anorectal sources, usually enlarged hemorrhoidal veins, can be identified easily during colonoscopy and account for less than 10% of acute lower intestinal bleeding *(57)*. Treatment by injection with epinephrine or a sclerosant, infrared coagulation, and band ligation of internal hemorrhoids is effective *(58)*, although more proximal etiologies should also be carefully excluded.

Interventional Radiology (Therapeutic Angiography)

Rapidly bleeding sites can be localized and treated by angiography if bleeding continues at the time of the exam. Disadvantages of this method include the requirement for availability of skilled interventional radiologists on very short notice, the need to move an unstable patient from the intensive care unit to a fluoroscopy unit, risks of contrast media allergic reactions or nephrotoxicity as a consequence of prolonged or repeated studies, and inherent complications of the invasive procedure.

The intermittent nature of GI bleeding in many patients poses a problem in angiography, because active bleeding at the time of contrast injection is required for a positive diagnostic study. Initial control of hemorrhage by angiotherapy is reportedly high (62–100%). However, because of the intermittent natural history of bleeding and the lack of any controlled clinical trials, these apparent success rates are difficult to evaluate. The known frequency of major complications (9–21%) and recurrent bleeding in the short term (16–50%) must be balanced against the uncertainty about the success rates that can be attributed to the angiotherapy intervention *(59–62)*.

Vasoconstrictors like vasopressin can be injected intraarterially to treat vascular lesions like angiodysplasias or diverticula-associated bleeding, but this technique is associated with major complications, including serious arrhythmias, myocardial or intestinal ischemia, pulmonary edema, and hypertension requiring treatment. Embolization with various agents is an alternative to vasoconstrictors also associated with a significant rate of complications, including abdominal pain and intestinal infarction. Transcather embolization may use gelatin sponges, microcoils, polyvinyl alcohol particles, and detachable balloons. The role of vasopressin or embolization therapy is most appropriately considered in patients who are poor surgical risks. Ischemic complications appear to be commoner when embolization is performed for

colonic rather than upper GI hemorrhage, because of the relatively sparse colonic collateral circulation. Intestinal infarction may occur in about 20% of lower GI embolizations *(59)*.

Surgery

Surgery is a consideration in patients with acute lower intestinal bleeding if the blood transfusion requirement is greater than 4 U within 24 hours, or when bleeding recurs *(63)*. However, the decision to proceed depends on risks related to age and comorbid disease. Surgery is reserved for treatment of a defined site of hemorrhage, or for diagnostic purposes when combined with intraoperative endoscopy. Localization of the site of bleeding can help avoid extensive surgical intervention with blind total colectomy. Directed segmental resection (i.e., left hemicolectomy) can be considered in a patient with persistent or recurrent bleeding attributed only to diverticular disease limited to the left colon. Substantial risks of rebleeding and mortality are associated with blind limited resection or emergency total abdominal colectomy, particularly in elderly patients. If the results of thorough diagnostic studies are negative and the blood loss is self-limited or, if chronic, can be maintained by oral iron supplementation, further evaluation and surgical intervention may not be necessary.

SUMMARY

American Society for Gastrointestinal Endoscopy guidelines on the management of lower GI bleeding *(49)* state that in most patients, colonoscopy is the procedure of choice in the diagnosis of active lower GI bleeding. Angiography is appropriate when colonoscopy cannot be performed or has not identified a site in the setting of active bleeding. Upper endoscopy is indicated when an upper GI bleeding source is suspected or evaluation of the colon has been negative. When other studies have failed to identify the bleeding source, small bowel lesions should be considered.

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13 Surgical Approach to Acute Lower Gastrointestinal Bleeding

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CONTENTS

INTRODUCTION

The acute lower gastrointestinal (GI) bleeder can be not only a challenging problem but a frustrating one as well. Up to 85% of lower GI bleeding stops spontaneously, with only 25% of the patients having a recurrent hemorrhage. It is those patients with persistent or recurrent bleeding in which surgical intervention becomes an issue. The appropriate timing of surgery and the appropriate procedure to perform are the focus of this chapter. Obviously, if the site of the bleed has been identified preoperatively, a segmental resection is the procedure of choice.

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However, in up to 10% of patients, the site cannot be identified preoperatively. In this situation, many issues must be taken into account to arrive at the appropriate treatment for the individual patient.

As covered in previous chapters, there are multiple etiologies of lower GI bleeding including upper GI bleeding and anorectal sources. Proper evaluation, as previously discussed, should be performed to assess for these sources. Treatment for those sources is not covered in this chapter. Also not addressed is the treatment of sources such as colon cancer or colitis. Instead, this chapter focuses on the acute colonic hemorrhage, which, in most cases, is from an angiodysplasia or diverticula.

TIMING OF SURGERY

When a patient presents with lower GI bleeding, resuscitation must be instituted immediately. It is rare for patients to be hemorrhaging so profoundly that they fail to respond to resuscitation. Although this scenario is rare, if these patients do remain persistently hypotensive in the face of aggressive resuscitation, then immediate surgery is indicated. More commonly, the patient stabilizes, and ample time is available for deciding on the need for surgical intervention. Although 85% of these patients do not need surgery, it is not possible to predict which patients will continue to hemorrhage or have recurrent bleeding. Thus, all patients must be aggressively prepared for surgery in case it is required.

Many factors play a role in the decision to intervene surgically, including the patient's hemoglobin levels and transfusion requirements, hemodynamic status, underlying medical problems, duration of bleeding, and number of bleeding episodes. Also, whether appropriate or not, the status of localizing the site of a patient's hemorrhage can often be a factor; some surgeons postpone surgery if the location has not been determined. For the self-limited bleed, this is not a problem; however, in the patient requiring ongoing transfusions, significant delays in surgical intervention may lead to increased morbidity and mortality. A balance must be struck between the low morbidity and mortality of operations when the site is clearly identified and the increased morbidity and mortality of ongoing hemorrhage and massive transfusion.

The number of acceptable transfusions prior to surgical intervention is not exactly mandated. Multiple studies *(1–3)* have demonstrated an increase in morbidity and mortality for those patients receiving more than 10 U of blood, especially if the patient has been hypotensive. In a study by Bender et al. *(2)*, the mortality for the group of patients who received more than 10 U of blood was 45%, compared with 7.7% in those receiving less than 10 U. This study surmised that the appropriate

timing for operative intervention in a patient with a lower GI bleed is after they have received 6 U of blood, but prior to receiving 10 U. Other investigators have an even lower threshold, recommending surgery after 4–5 U of blood have been given in a 24-hour period *(4–7)*.

More detailed guidelines have been laid out by authors such as Nahrwold *(8)*, who recommends the following indications for operative intervention: (a) if 1500 mL of blood is necessary to accomplish resuscitation and bleeding continues; (b) if 2000 mL of blood is necessary to maintain vital signs during a 24-hour period; (c) if bleeding fails to resolve within 72 hours; and (d) if rebleeding occurs within 1 week of cessation of a significant hemorrhage.

Most surgeons agree that recurrent bleeding, especially during the same hospital admission, is an indication for surgery. This decision, of course, is easier if the site of bleeding has been localized and therefore a segmental resection can be performed, or if the episodes of hemorrhage are severe. Some investigators support conservative management of most recurrent bleeding, as they cite only a 50% rate of rebleed for a third time *(9)*. Most surgeons, however, proceed with operative intervention at the time of recurrent bleeding.

A subset of patients does exist who have repeated episodes of hemorrhage, which require minimal transfusions and are spaced in time by different hospitalizations. Surgery for a nonlocalized bleed in these patients is less compelling. Instead, one should more aggressively pursue the source of the bleed, keeping in mind that it may be from the small bowel. The nonemergent nature of the bleed allows for this more extensive and necessary workup and may prevent a nontherapeutic total colectomy.

Another subset of patients are those who have their bleeding site localized by angiography and then their bleeding subsequently stops or is aided in its cessation by vasopressin or embolization. Some surgeons are proponents of nonoperative intervention at this point in the same way that a noncomplicated diverticulitis patient is allowed one episode, with surgery only recommended after a second attack. A rebleed rate of only 25% in all cases is cited in support of this opinion, even though the rebleed rate in this subgroup may be higher. Other surgeons, including the authors, disagree with that stance. Obviously, bleeding that can be localized by angiography is severe. A rebleed of this type would be life-threatening. Intervention at the time of the first bleed is therefore advised. Some may argue that vasopressin or embolization is adequate intervention, but the rebleed rate is significant, with an approximately 30% rebleed rate after successful vasopressin therapy *(10–12)* and a 25% rebleed rate after successful embolization *(13–16)*. Thus, the over-

all need for eventual surgery in this group is closer to 35–40%. Therefore, it is the opinion of many, including the authors, that a patient with a lower GI bleed localized by angiography should have a segmental resection if he or she is deemed an operative candidate.

In general, the accepted indications for operative intervention of the lower GI bleed include an immediate life-threatening hemorrhage, persistent hypotension, transfusion requirements exceeding 4–6 U within a 24-hour period, and rebleeding, especially within the same hospitalization. One must keep in mind the increased morbidity and mortality that can result if surgery is postponed too long or if an unnecessary blind resection is performed. Obviously, the patient's overall health status is important in balancing this decision, as elderly or frail patients are unable to tolerate blood loss as well as young healthy individuals, and therefore early operative intervention should be considered. Unfortunately, the surgeon often postpones operating in the hope that the bleeding will stop, thereby avoiding a major surgery on a higher risk patient. This tactic, however, contributes to a higher mortality in this group and is therefore strongly discouraged.

THE APPROPRIATE OPERATION

In most cases, by the time the decision has been made to take the patient to the operating room for a lower GI bleed, the patient has been through various diagnostic tests in an attempt to localize the source of the bleeding. These tests and their accuracy are described in a previous chapter. Briefly, the typical diagnostic algorithm of the authors is to first rule out an upper GI source by placing a nasogastric tube and irrigating until bile returns. Next, a proctoscopy is performed to assess for an anorectal etiology. If this is negative, one proceeds with a tagged red blood cell scan (bleeding scan). If the bleeding scan is negative, a colonoscopy is performed. If the bleeding scan is positive, with an immediate blush, then angiography is performed. If angiography is positive, then the site of the bleed is considered to be localized. If it is negative, colonoscopy is performed. There are some high-quality cine bleeding scans that can be considered localizing and that must be assessed on an individual basis. For a colonoscopy to be considered localizing, active bleeding from the site must be witnessed.

Most patients requiring surgery will have their bleeding source localized and, of course, a segmental resection is most appropriate. However, in at least 10% of patients *(17)*, the source remains elusive at the time of surgical intervention. It is in this group of patients that the choice of an appropriate procedure becomes more challenging.

THE LOCALIZED BLEED

Even in those patients in whom the bleeding is considered to be localized accurately preoperatively, some studies show a rebleed rate up to 5.2% *(9)*, whereas other authors demonstrate no recurrent bleeding *(18)*. Obviously, if the patient is stable enough for a bowel prep, this is preferred. However, if time does not allow, lack of a formal prep does not exclude a primary anastomosis. Since blood is a cathartic, the GI bleeder has, to some extent, performed a self-prep. Intravenous antibiotics are given at the time of surgery, and then an exploration is carried out prior to the segmental resection. If the patient is not hypotensive and does not have extensive comorbidities or other obvious contraindications, a primary anastomosis is preferred. However, creation of an ileostomy or colostomy is acceptable in less hemodynamically stable patients.

Laparoscopically assisted colectomies are increasing in popularity. For the surgeon who is skilled in this technique, it is reasonable to proceed with a laparoscopic approach in the stable, localized patient. Because of the increased setup time, it is not advised in the hemodynamically labile patient. Also, it would not be recommended for the nonlocalized bleeder.

THE NONLOCALIZED BLEED

The nonlocalized bleeder is, of course, more difficult to manage. As mentioned previously, delaying surgery secondary to nonlocalization of the bleeding adds significant morbidity and mortality to this group of patients. Thus, even if the site of bleeding has not been localized, one should proceed with surgery at the appropriate time. In the past, some surgeons advocated a transverse loop colostomy or ileostomy to help localize the site of bleeding by following the effluent for blood. This technique, however, is rarely used today; the current surgical options are blind left colectomy, blind right colectomy, or blind total colectomy.

Once the patient is taken to the operating room, attempts to localize the bleeding site continue. The patient is placed in a modified lithotomy position, and an exploration is performed looking for an obvious source such as a mass or perhaps a Meckel's diverticulum. Usually exploration does not yield a source of the bleeding. Clues may be gained to increase one's awareness of a possible small bowel bleed such as an extensive amount of blood in the small bowel. This finding, however, does not ensure a small bowel source. If the patient is relatively stable, one can perform intraoperative colonoscopy and enteroscopy as a final attempt

to localize the source prior to a blind resection. These further attempts at localization may not be feasible at many institutions owing to lack of resources, especially if the surgery is being performed in the middle of the night.

BLIND LEFT COLECTOMY

Up until the 1950s, most lower GI bleeding was felt to be secondary to diverticulosis. Since the left colon was the predominant location of diverticula, surgeons supported segmental resection of the left colon in cases of persistent lower GI bleeding. This approach resulted in a high rebleeding rate of 30% *(9,19)*, as well as a high mortality rate of 20–40% *(4,20–22)*. These poor results were largely because of the unrecognized right-sided angiodysplastic lesions as a common cause of lower GI bleeding. A shift occurred in the 1950s toward total abdominal colectomies for lower GI bleeding followed later by a shift to blind right colectomies, with the justification that most lower GI bleeds are from the right colon. Currently, a blind left colectomy for lower GI bleeding is discouraged, although some surgeons will selectively perform one based on intraoperative findings such as blood limited to the left colon. This obviously is not a foolproof method by which to make a decision and therefore is not the standard of care.

BLIND RIGHT COLECTOMY

In looking at the high rebleed rate from blind left colectomies, the source of bleeding was questioned further. Angiodysplasias, which are usually located in the cecum and ascending colon, were recognized as one source of bleeding. Also, even though most colonic diverticula are located in the left colon, studies demonstrated that 60% of diverticula confirmed by angiography to be the site of lower GI bleeding were proximal to the splenic flexure *(3,6,23,24)*. This new information led many to support the blind right colectomy for nonlocalized lower GI bleeding. The argument for this approach could be strengthened for an individual patient if no left-sided diverticula were noted or a negative colonoscopy exam of the left colon had been performed *(2)*. Some argue for a right colectomy if blood is primarily in the right colon, but since the flow does proceed retrogradely, as well as antegradely, too much emphasis should not be placed on this finding. Obviously, a benefit of a right colectomy is the decreased risk of diarrhea or incontinence postoperatively.

In their paper supporting blind right colectomies, Milewski and Schofield *(9)* pooled data from 27 series. They then compared the mor-

tality and rebleed rates of three separate groups: blind right colectomy, blind left colectomy, and blind total colectomy. The mortality rate was lowest for the right colectomy group, at 5.2%, compared with 31.6% for the left colectomies and 16.1% for total colectomies. The rebleed rate, however, was lowest for the total colectomy group, at 2.1%, compared with 19.2% for the right colectomy group and 38% for the left colectomy group (Table 1). They argued, though, that the higher rebleed rate with the blind right colectomy did not increase the mortality in this group and thus was the preferred management. If the patient rebleeds, then a completion total colectomy is indicated unless a small bowel source is discovered. This study is commonly cited for those supporting a blind right colectomy. However, the study was a pool of various studies from the literature, and important information (such as the number of blood transfusions in each group) was not included. The variability and lack of information make its conclusions much less reliable. Even accepting the data from this study, one should keep in mind that Milewski and Scholfield's *(9)* recommend a blind right colectomy only when other findings are suggestive of a right-sided source, such as blood found only in the right colon. The yield in doing a right colectomy is improved by extending the resection to include the transverse colon, but, again, the support for this blind resection is questionable.

BLIND TOTAL COLECTOMY

The total abdominal colectomy for nonlocalized lower GI bleeds was popularized in 1953 by Cate *(25)*, who reported a single case for which he had performed a total colectomy after the patient had multiple episodes of bleeding and 16 U of blood transfused. The patient's recovery was uneventful. Based on this single case report, total colectomy for lower GI bleeding became the standard practice for the subsequent two decades. Multiple studies *(20,26,27)* published during that time supported total colectomy as the procedure of choice in nonlocalized lower GI bleeds. One of the most notable was that of Drapanas et al. *(20)*, which showed a mortality rate of only 11% for those patients undergoing total colectomy, compared with 30% in those patients having a limited resection.

Later reports in the 1970s and 1980s purported to show a higher mortality rate associated with total colectomy *(5,28,29)* than previous studies, and thus the shift to blind segmental resection occurred at that juncture. This increased mortality, however, may have been related to delays in surgery for patients receiving higher numbers of transfusions.

Table 1
Mortality and Rebleeding Rates for Different Surgical Techniques

Study	*Blind resection*	*No. of patients*	*Mortality rate (%)*	*Rebleed (%)*
Farner et al., 1999 *(32)*	Segmental resection	50	7.0	18.0
	Total colectomy	27	2.0	4.0
Milewski and Schofield, 1989 *(9)*	Right colectomy	78	5.2	19.2
	Left colectomy	92	31.6	38.0
	Total colectomy	94	16.1	2.1
Eaton et al., 1981 *(22)*	Segmental resection	24	50.0	75.0
	Total colectomy	4	0.0	0.0
Drapanas et al., 1973 *(20)*	Segmental resection	28	30.0	35.0
	Total colectomy	35	11.0	0.0

Recent studies have shifted the tide again toward total colectomy, as the mortality and morbidity rates have been demonstrated to be low (0–6%) *(30–32)*. Farner et al. *(32)* reported one of the largest series, with 77 patients requiring laparotomy for acute lower GI bleeding. Not only did they show a comparable mortality in the total colectomy group of 2% compared with 7% in the limited resection group, they also demonstrated a lower rebleed rate of 4% compared with 18%, with no difference in morbidity. Diarrhea was not an issue with the total colectomy group, which averaged 1.9 bowel movements a day. Multiple other studies *(29–31)* also report no problems with diarrhea or incontinence in their total colectomy group.

As with segmental resections, a primary anastomosis can be performed with a total colectomy in the stable patient who does not have significant morbidities. This anastomosis, of course, would be ileorectal. For the patient who was incontinent preoperatively or has very poor sphincter tone, an end ileostomy is advisable.

ALGORITHM FOR TREATMENT OF LOWER INTESTINAL BLEEDING

Our current approach to lower GI hemorrhage is outlined in Fig. 1. Patients undergo initial assessments of fluid status and comorbidities for surgery. They undergo resuscitation with fluids and blood transfusions, as required, and are prepared for surgical therapy should this become necessary. Hemoglobin and hematocrit, electrolytes, coagulation profile, liver function tests, and kidney function tests are performed. Adequate resuscitation and correction of fluid and electrolyte balance are important not only for future surgical intervention, but also for diagnostic tests, which may require intravenous contrast and/or sedation.

If the patient does not respond to resuscitation, he or she should be taken to the operating room, where a total colectomy should be performed. Patients who respond should undergo localizing studies. The type and number of studies vary and must be individualized for each patient. Patients who have their site of bleeding identified and who have ongoing bleeding should have a segmental resection. Patients who exhibit persistent hemorrhage but do not have localization of their site of bleeding should undergo total colectomy.

Patients who stop bleeding spontaneously, whether localized or not localized, should undergo colonoscopy to exclude neoplasms or angiodysplasias that require further therapy.

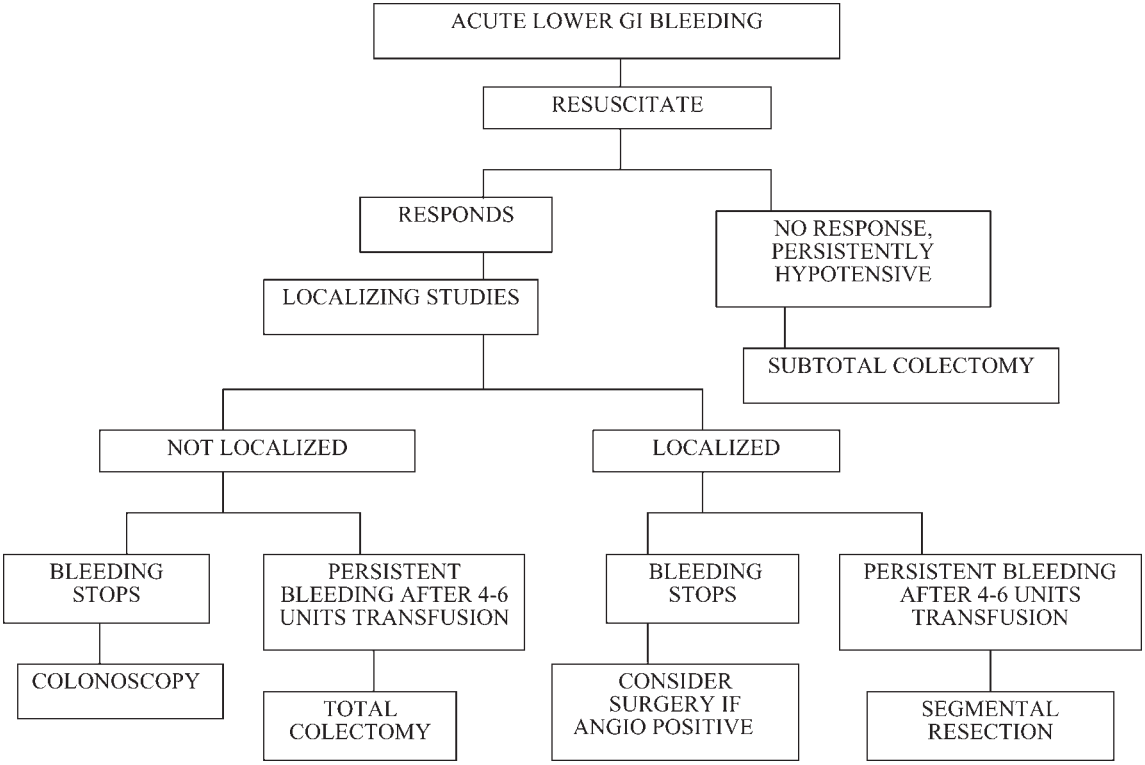

Fig. 1. Algorithm for treatment of lower GI bleeding.

SUMMARY

Fortunately, most acute lower GI bleeding is self-limited and resolves spontaneously.

Indications for operative intervention are an immediate life-threatening hemorrhage, persistent hypotension, transfusion requirements exceeding 4–6 U within a 24-hour period (and less than 10 U total), and rebleeding, especially within the same hospitalization.

With the advances in diagnostic modalities, approximately 90% of patients will have their site of bleeding localized, allowing for a segmental resection. A laparoscopic approach is reasonable in this group of patients as long as they are stable and the surgeon is proficient with laparoscopic exploration and colectomies. In the patient with the nonlocalized bleed in which a total colectomy is indicated, a laparoscopic approach is not advisable.

For the 10% of patients whose bleed is not localized, total colectomy is the procedure of choice of most surgeons as it offers the lowest recurrence rates, approaching zero, with mortality rates equivalent to those for segmental resections. It appears that rebleeding is a larger threat to the patient than a more extensive operation. The keys to low morbidity and mortality are (a) adequate resuscitation of the patient and avoidance of hypotension; (b) localization of the site of hemorrhage in as many patients as possible; (c) expeditious surgery; and (d) an operation that definitively addresses the hemorrhage. Clearly, a balance must be achieved between localization of the site of hemorrhage and expeditious surgery, but reluctance to proceed with surgery because of a failure to localize the site of the bleed adds unnecessary delays to the patient's care, resulting in higher transfusion requirements and increased morbidity and mortality.

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14 Radiologic Evaluation and Intervention in the Acute Gastrointestinal Bleed

Charles A. Owens, MD

Contents

INTRODUCTION

Each year, acute gastrointestinal (GI) bleeding is responsible for 1–2% of all hospital admissions within the United States *(1)*. In the United Kingdom, GI hemorrhage accounts for up to 8% of emergent medical admissions and 6000 annual deaths *(2)*. Hemodynamic stabilization is the primary objective in the initial management of acute GI hemorrhage.

Prediagnostic Workup

Intravenous access is established with at least two large-bore peripheral sites and/or a central venous catheter to allow rapid expansion of intravascular volume. Replacement of blood components should begin if hemodynamic stability cannot be maintained after 2–3 L of normal saline has been given *(3)*.

From: *Acute Gastrointestinal Bleeding: Diagnosis and Treatment*
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Physicians caring for patients with GI hemorrhage must be aware of common pitfalls encountered during clinical assessment and management. For example, early in the event of a major hemorrhage, the hematocrit may not reflect the profound blood loss that the patient has suffered. In addition, a patient who is taking oral β-blockers may not demonstrate tachycardia, even in the face of severe hypovolemia, confusing the clinical picture. Following a massive infusion of crystalloid and packed red blood cells (RBCs), a transfusion coagulopathy may occur whenever clotting factors and platelets are not concurrently given. Such a deficiency of coagulation factors may prolong and intensify ongoing hemorrhage.

While the patient is being resuscitated, and after a thorough but brief history and physical examination has been obtained, the gastroenterologist should be consulted for an emergent upper or lower endoscopic examination. Although most cases of acute GI hemorrhage can be diagnosed and treated by endoscopy, upper endoscopy remains nondiagnostic in up to 10% of patients, and emergent colonoscopy will fail to identify the lesion in up to 40% of lower GI hemorrhages *(4–6)*. Endoscopic therapy also fails to control GI bleeding in up to 20% of cases *(7,8)*. Radiologic modalities, both diagnostic and interventional, can provide an important supplement to the localization and management of acute GI hemorrhage.

ACUTE GASTROINTESTINAL HEMORRHAGE

Acute Upper Gastrointestinal Hemorrhage

In the United States, more than 300,000 annual hospital admissions can be attributed to upper GI bleeding *(9)*. Although bleeding will stop spontaneously in most cases, persistent or recurrent bleeding accounts for the associated 5–12% mortality rate *(10,11)*. In patients who are older than 60 years and/or have cirrhosis, the mortality rate increases dramatically *(11)*.

The causes of upper GI hemorrhage (Table 1), in order of decreasing frequency, are peptic ulcer disease (Fig. 1), portal hypertensive variceal bleeding (Fig. 2), Mallory-Weiss tears, angiodysplasias, gastric neoplasms, and erosive gastritis/esophagitis *(11)*. Despite medical advances in prevention and management, peptic ulcer disease remains the most common cause of bleeding in the upper GI tract, accounting for almost half of all cases presenting with severe hemorrhage *(12–15)*.

Esophagoduodenoscopy (EGD) is the preferred initial examination (Fig. 3) to identify upper GI sources of bleeding because it has the potential to provide immediate diagnosis and therapy *(15)*. Thermal

Table 1
Etiology of Acute
Upper Gastrointestinal Hemorrhage

Esophagus
Esophageal varices
Mallory-Weiss tear
Esophagitis
Stomach
Dieulafoy's lesion
Gastric ulcer
Hemorrhagic gastritis
Duodenum
Duodenal ulcer
Hemobilia
Aortoenteric fistula

coagulation therapy and/or injection of a vasoconstrictive agent into an actively bleeding ulcer or visible vessel have been shown to reduce the rate of rebleeding significantly *(16,17)*. When endoscopy fails to identify or control the source of bleeding, the assistance of interventional radiology and/or surgery may be required.

Acute Lower Gastrointestinal Hemorrhage

Lower GI hemorrhage accounts for 10% of all acute GI bleeding, with 70% occurring in patients older than 65 years *(18)*. Although the origin of bleeding depends largely on the age of the patient and the rate of hemorrhage, the two most common causes of massive lower gastrointestinal hemorrhage are diverticular disease (Fig. 4) and angiodysplasias (Fig. 5) (Table 2) *(9)*. Less common etiologies include ischemic colitis, neoplasms, Meckel's diverticulum, inflammatory bowel disease, postpolypectomy bleeding, and a wide range of AIDS-associated conditions such as Kaposi's sarcoma (Fig. 6), lymphoma, and cytomegalovirus ulcers *(19,20)*.

In adults, diverticular disease is the source of 30–40% of major lower GI hemorrhage *(4,5,21,22)*. Although most episodes of diverticular hemorrhage cease spontaneously, up to 35% will require blood transfusion and 5% an emergent operation *(23,24)*. Following the first episode of bleeding, there is a 25% chance of reoccurrence, and after two episodes of hemorrhage, the risk of rebleeding approaches 50% *(25)*.

Diverticula occur where branches of the vasa recta penetrate the bowel wall to supply the mucosa, creating an area of weakness within the muscularis. The mucosa herniates through these sites of weakness, form-

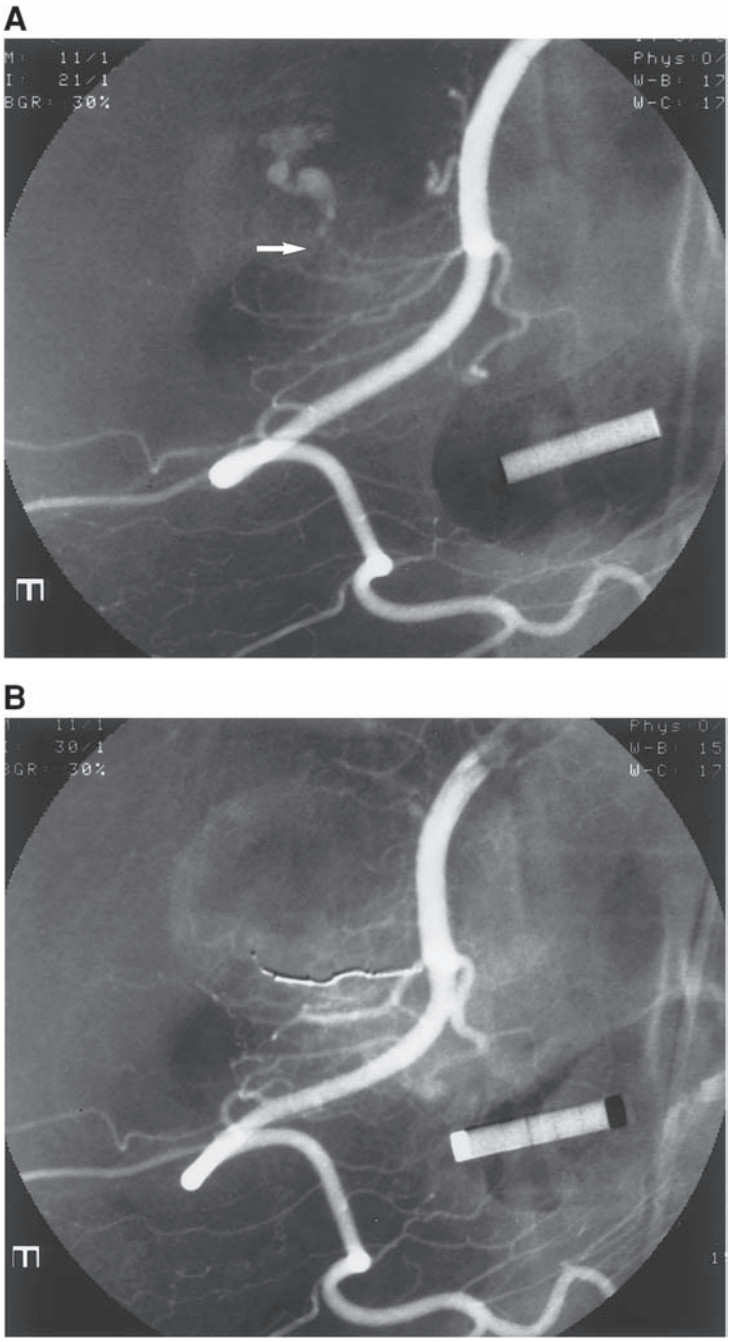

Fig. 1. Duodenal ulcer hemorrhage. **(A)** Selective gastroduodenal arteriogram in a 43-year-old man with massive upper gastrointestinal bleeding demonstrates hemorrhage (arrow) from a duodenal bulb ulcer. **(B)** Bleeding was controlled after superselective embolization of the feeding branch artery with microcoils.

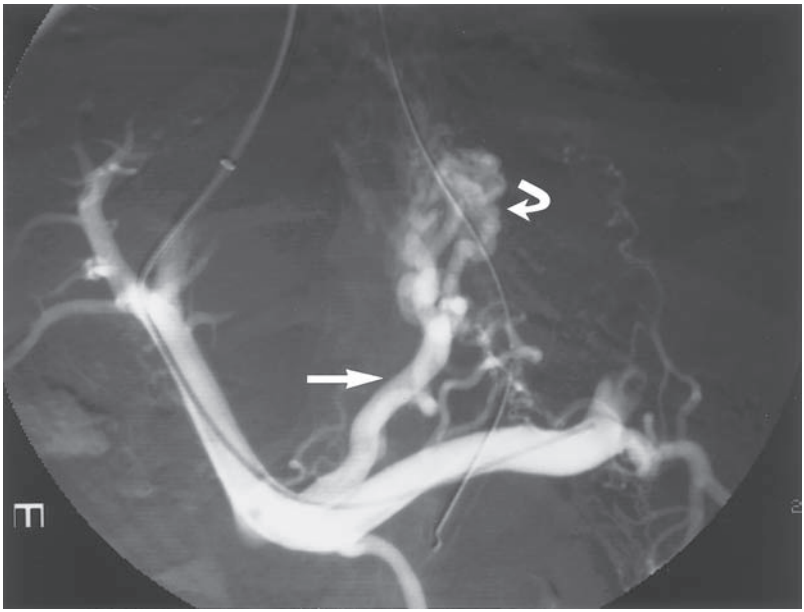

Fig. 2. Direct portography demonstrating portal hypertension. Selective transhepatic portography, prior to a TIPS procedure, demonstrates hepatofugal blood flow in a large coronary vein (straight arrow) feeding gastroesophageal varices (curved arrow).

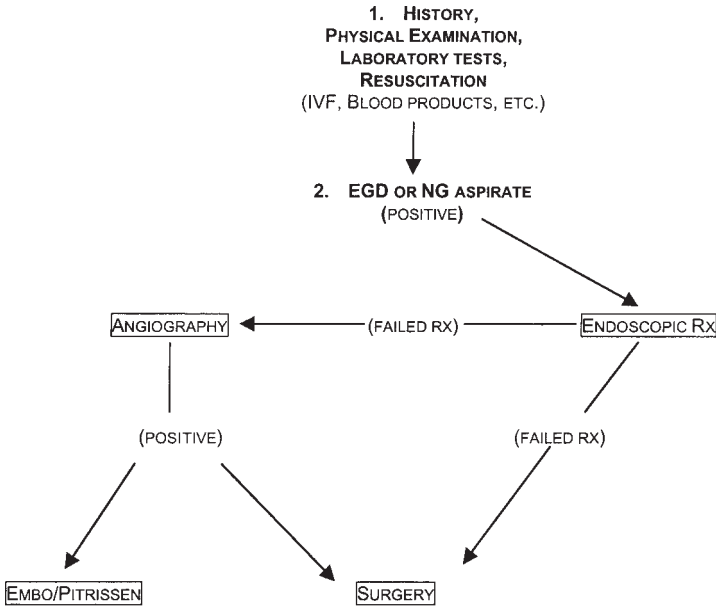

Fig. 3. Proposed algorithm for evaluation of acute upper gastrointestinal bleeding. EGD, esophagoduodenoscopy; IUF, intravenous fluids; NG, nasogastric.

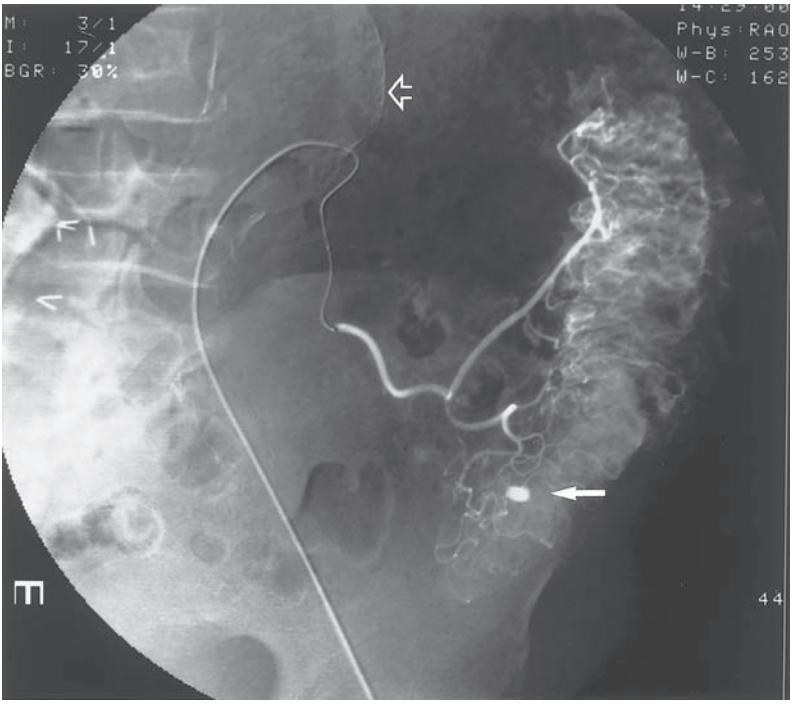

Fig. 4. Colonic diverticular hemorrhage. Selective inferior mesenteric arteriogram, in a 77-year-old man with an abdominal aortic aneurysm (open arrow), shows contrast pooling in a bleeding diverticulum (solid arrow).

Table 2
Etiology of Acute Lower Gastrointestinal Hemorrhage

Small bowel
Angiodysplasia
Tumor
Inflammatory bowel disease
Colonic
Diverticulosis
Angiodysplasia
Tumor
Inflammatory bowel disease
Meckel's diverticulum
Ulcers (CMV)
Ischemic colitis

Abbreviation: CMV, cytomegalovirus.

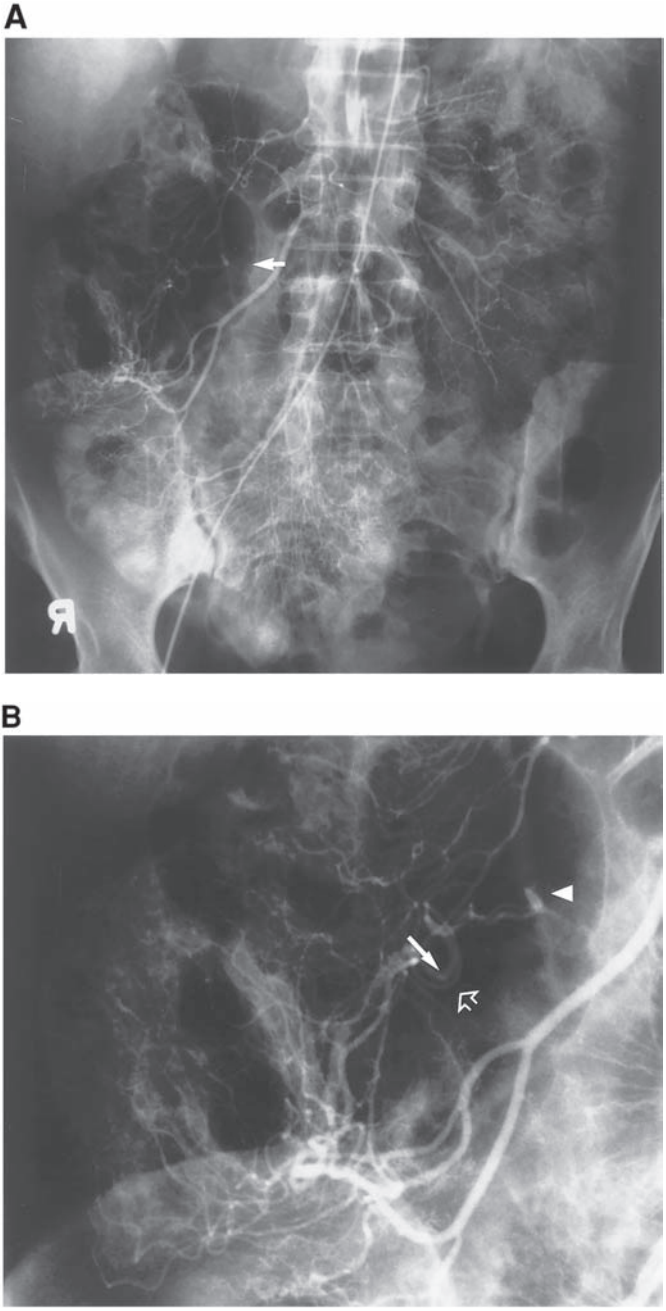

Fig. 5. Colonic angiodysplasia. **(A)** Superior mesenteric arteriogram showing angiodysplasia (arrow) arising from the right colonic artery. **(B)** Magnified view of the same image better demonstrates the subtle findings of a vascular tuft (arrowhead), the feeding artery (open arrow), and the enlarged draining vein (solid arrow).

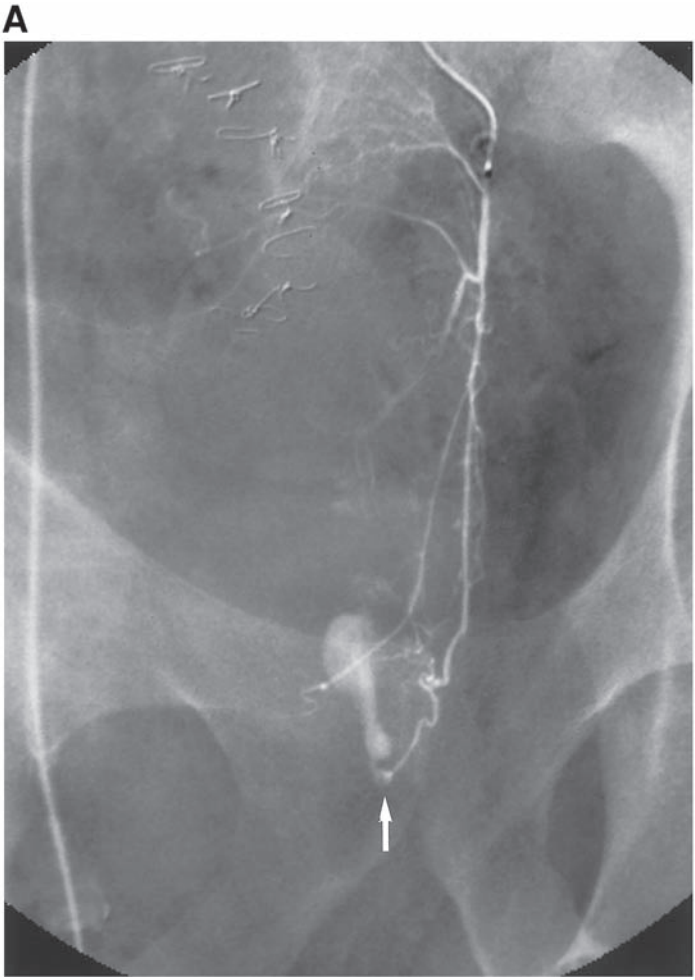

Fig. 6. Rectal tumor hemorrhage. **(A)** Selective inferior mesenteric arteriogram, in a 52-year-old man with HIV infection, demonstrates extravasation (arrow) from a Kaposi's sarcoma. Massive hemorrhage was controlled by superselective embolization of the tumor with polyvinyl alcohol (PVA), allowing stabilization prior to surgery.

ing pseudodiverticula *(18,26)*. A rich supply of blood vessels coursing over the dome of the diverticulum is exposed to trauma and bleeding. Although most diverticula are located in the left colon, *(27)* most diverticular bleeding occurs on the right *(28,29)*.

In contrast with upper GI hemorrhage, the role of endoscopy in localizing and treating lower GI sources is not well established (Fig. 7).

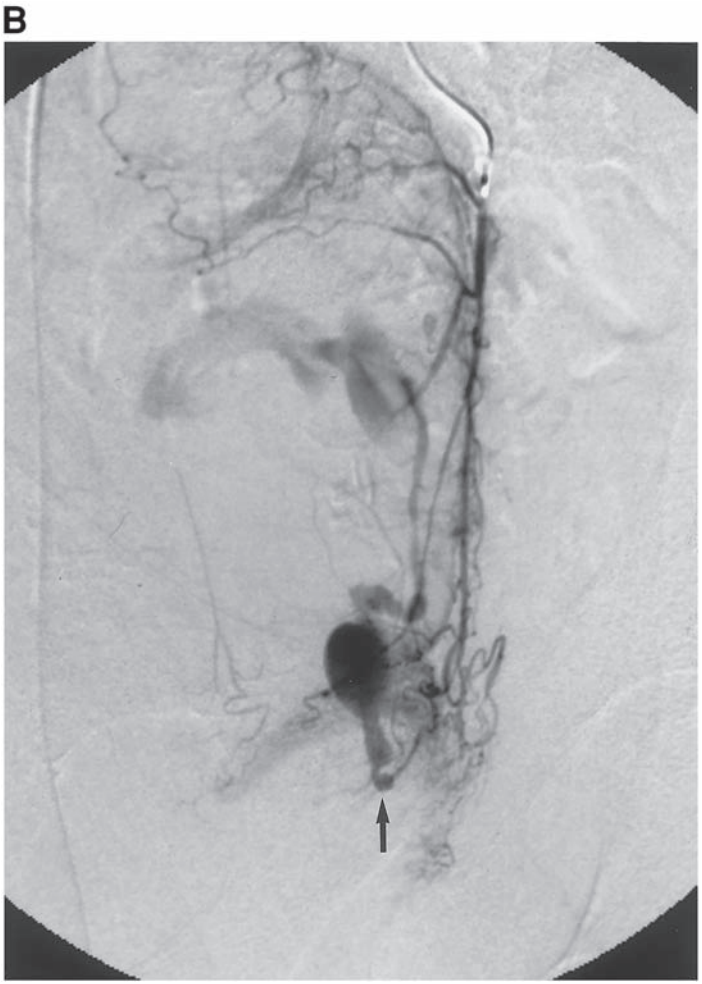

Fig. 6. *(continued)* **(B)** Digital subtracted image during the same run. (Case contributed by Dr. Amjad Alkadri, University of Illinois Medical Center at Chicago.)

Lower GI bleeding is often intermittent and can arise from locations within the small bowel that are inaccessible to routine endoscopic examination. Some authors have recommended push or pull endoscopy, or interoperative enteroscopy to evaluate the small bowel. These more invasive techniques require more elaborate equipment and skills and are not available at most institutions.

Most episodes of lower GI bleeding stop spontaneously; however, 10–25% will require some form of intervention *(30)*. In a review of

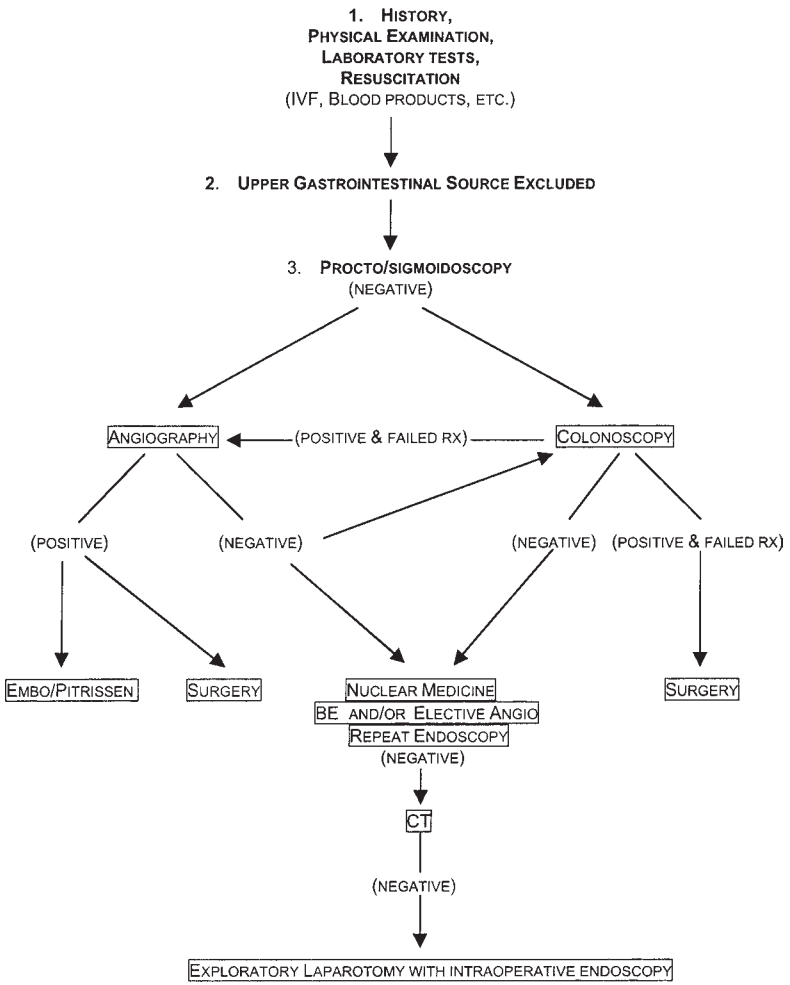

Fig. 7. Proposed algorithm for evaluation of acute lower gastrointestinal bleeding. BE, barium enema; IVF, intravenous fluids.

104 patients with lower GI bleeding, McGuire *(31)* demonstrated that one can predict which patient would be likely to need surgery based on his or her transfusion requirements. In 99% of patients who were given less than 4 U of blood within a 24-hour period, the bleeding stopped spontaneously. When four or more units of blood were given within the same amount of time, 60% of patients required emergent surgery *(31)*.

Identifying the bleeding site prior to surgery allows for accurate segmental resection, lowering the morbidity and mortality of an undirected total colectomy *(32–35)*. Presurgical localization of the bleeding can

lower the 40% operative mortality rate of an emergent subtotal colectomy to a 13% mortality associated with a directed segmental resection *(21)*. Angiography is reported to be accurate in detecting lower GI bleeding in 40–92% of cases *(21,30,33,36)*. The reported sensitivity and accuracy of nuclear medicine bleeding scans is 30–98% and 52–95%, respectively *(37–43)*. Preoperative and intraoperative identification of small bowel sources of bleeding can be very challenging. When the source of hemorrhage is localized to the small bowel, the interventional radiologist can assist surgery by retaining a small 2.5–3.0-Fr coaxial microcatheter as close as possible to the bleeding site (Fig. 8B). The catheter is left on a saline infusion pump as the patient is transported to the operating suite. While the small bowel is being examined in the operating field, methylene blue is injected into the catheter to identify the affected segment of bowel and to guide conservative surgical resection *(44–46)*.

Chronic Obscure Gastrointestinal Hemorrhage

In a small group of patients, despite a battery of diagnostic tests, including upper and lower endoscopy, the source of bleeding remains obscure. This subset of GI hemorrhages represents a considerable diagnostic challenge to the primary physician. By definition, obscure bleeding can be *occult* (recurrent iron deficiency anemia and/or recurrent positive fecal occult blood test) or *overt* (recurrent passage of visible blood) in its presentation *(47)*. Although single- and/or double-contrast (enterocolysis) barium examinations of the small bowel uncover many neoplastic or inflammatory causes of obscure bleeding, in approximately 5% of cases the source will remain obscure *(48)*. Diagnostic mesenteric arteriography can be helpful in identifying angiodysplasia (Fig. 5) or other vascular anomalies. After identification, the lesion can be embolized, or a coaxial microcatheter can be positioned near the malformation and used for intraoperative localization *(46,49)*.

Some authors have recommended the use of carbon dioxide arteriography or infusion of 99m Tc colloid directly into the superior or inferior mesenteric artery in an attempt to enhance detection of obscure GI bleeding *(50,51)*. Others have advocated provocative measures such as heparinizing the patient prior to angiography, or infusing vasodilators (vasopressin) or thrombolytics (recombinant tissue plasminogen activator) directly into the suspected artery at the time of the angiogram *(52–57)*. These provocative maneuvers are an attempt to induce bleeding to improve the diagnostic yield of angiography and allow identification and treatment of the offending lesion. Such techniques are associated with an increase in transfusion requirements and other com-

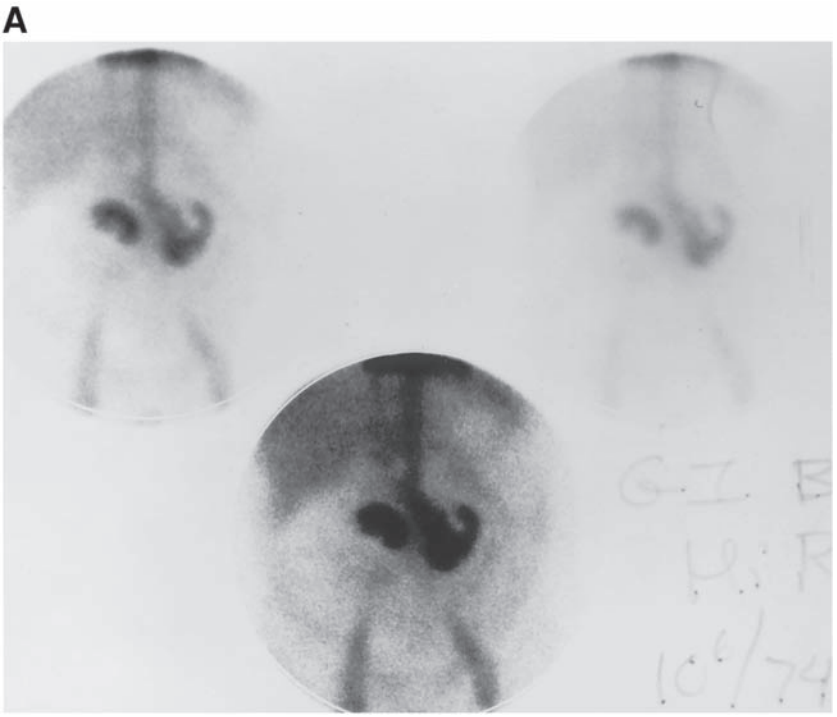

Fig. 8. Small bowel hemorrhage. **(A)** 99m Tc RBC nuclear medicine study in a 79-year-old man with massive lower gastrointestinal bleeding identifies hemorrhage in the mid small bowel.

plications and should be reserved for stable patients with recurrent GI bleeding that have failed identification by other less invasive means *(53)*.

DIAGNOSIS/LOCALIZATION

A clinical distinction must be made between an upper versus a lower GI source of bleeding. The ligament of Treiz is a muscular fibrous band that separates the jejunum from the fourth portion of the duodenum. It is this anatomic marker that divides the upper from the lower GI tract. Up to 90% of acute GI bleeding arises from a source proximal to the ligament of Treiz, and most of these patients will have a positive nasogastric aspirate *(58)*. Placement of a large-bore nasogastric tube can therefore be very helpful in determining the probable source and amount of bleeding. Approximately 10% of patients with an upper GI source of hemorrhage will have a falsely *negative* nasogastric lavage *(9)*. When the nasogastric aspirate contains neither blood nor bile, then

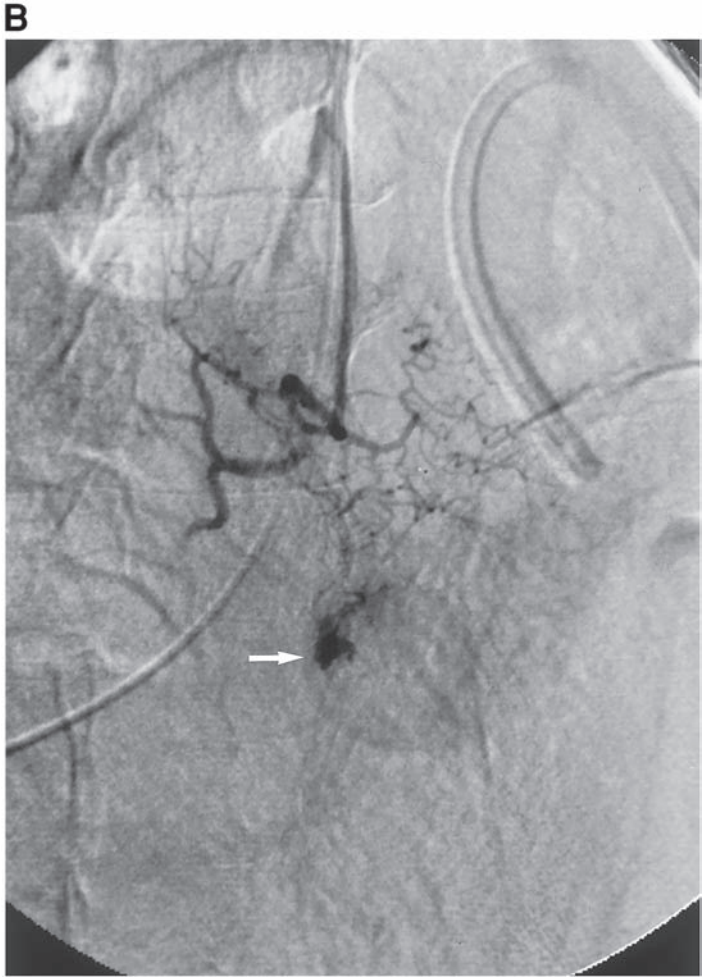

Fig. 8. *(continued)* **(B)** Selective superior mesenteric arteriogram, through a 3-Fr coaxial microcatheter, placed as close to the hemorrhage as possible, identifies the extravasation (arrow). The catheter is not superselective enough for safe embolotherapy. Instead, methylene blue is injected through the 3-Fr microcatheter to identify the affected bowel segment just prior to surgical resection.

an obstruction of the pylorus, which may be caused by a large duodenal or pyloric channel ulcer, should be suspected *(1)*.

A black "coffee ground" type of material, coming from an upper GI source of bleeding, is the result of gastric acid converting hemoglobin into acid hematin *(1)*. Since it requires time for this alteration to occur,

aspirating "coffee ground" material usually suggests a slower rate of hemorrhage, whereas aspiration of bright red blood indicates rapid, ongoing bleeding. If the nasogastric aspirate fails to clear after lavaging 2–3 L of tap water, then persistent massive bleeding is indicated, and emergent intervention is required.

Rectal bleeding can result from an upper or lower GI hemorrhage. In up to 10% of patients presenting with severe rectal bleeding, the source arises proximal to the ligament of Treitz *(59)*. In general, blood from an upper intestinal source produces a black tarry stool; however, the bleeding can be so brisk and the motility through the bowel so fast that it will present as bright red blood *per rectum*. Bleeding from a colonic source typically will present as rectal bleeding that is bright red and not thoroughly mixed with the stool *(60)*.

Endoscopy should be performed prior to angiography, as 80–90% of massive upper GI bleeding can be controlled through endoscopic or conservative means *(8)*. "Search and destroy" (total body) angiographic procedures should be avoided. Endoscopic findings, even when negative, can be used to direct angiography, limiting the amount of iodinated contrast used and increasing the sensitivity of the study *(61)*. In patients with cirrhosis, it is important that endoscopy always precede angiography. Although secondary signs of portal hypertension can be seen on arterial portography (Fig. 2), acute variceal bleeding is rarely, if ever, demonstrated.

Radiographic examinations using barium (i.e., small bowel follow-through, enterocolysis) may be of some benefit in evaluating small bowel sources of recurrent or chronic hemorrhage; however, such studies have no part in the management of acute bleeding. In the initial workup of acute GI hemorrhage, single- and double-contrast barium studies are insensitive and provide no therapeutic advantage. The presence of barium within the bowel precludes the use of arteriography and nuclear studies and interferes with endoscopy *(62)*.

Nuclear Medicine

When the bleeding appears to be intermittent or has decreased to the point that other diagnostic studies would probably be insensitive, then nuclear medicine scintigraphy should be considered. Compared with arteriography, nuclear medicine studies are more sensitive at detecting slower or intermittent rates of bleeding. Animal studies have indicated that nuclear medicine bleeding scans can detect rates as low as 0.04 mL/min and total volumes as small as 2–3 mL *(63,64)*. In clinical practice, however, studies have suggested that slightly greater rates of bleeding are required for a positive study *(37)*.

The two radionuclide agents used in nuclear medicine bleeding scans are technetium-99m-labeled sulfur colloid (Tc99m-SC) and technetium-99m-labeled erythrocytes (Tc99m-RBC). Both agents circulate in the intravascular space and localize bleeding by extravascular accumulation (Fig. 8). Although Tc99m-SC is easier to prepare and more sensitive than Tc99m-RBC at identifying slower bleeding rates, Tc99m-SC has a shorter intravascular half-life (12–15 minutes), making it less of an optimal choice for intermittent bleeders. Tc99m-SC also accumulates in the spleen and liver, obscuring the identification of bleeding within both upper quadrants.

Studies have reported that approximately 70% of nuclear medicine bleeding scans require more than 2 hours of imaging to demonstrate a bleeding site, implying that most GI bleeding is intermittent in nature *(65,66)*. Tc99m-RBC, in contrast to Tc99m-SC, remains within the intravascular space and may detect bleeding 24 hours after injection *(38)*. If close follow-up imaging is not obtained, then accurate localization of the bleeding source can be severely compromised by anterograde and retrograde migration of the radiotracer. Bowel peristalsis can carry the radiotracer well beyond the point of bleeding, creating a diffuse pattern of uptake throughout the GI tract. Suzman et al. *(67)* have suggested that the accuracy of bleeding scans can be greatly enhanced by acquiring dynamic images at 5-minute intervals during the first hour, followed by 15-minute intervals for the following 3 hours. When necessary, additional images are obtained every 90 minutes for the remaining 20 hours *(67)*.

The value of nuclear medicine bleeding scans as a screening tool for acute GI hemorrhage, is unclear, and opinion regarding its utility is widely divergent *(38)*. Some authors have promoted it as a minimally invasive and cost-effective tool that is highly accurate at localizing bleeding sites and therefore should be used as the primary imaging modality to direct surgical intervention *(21,65,68)*. Other investigators have found that nuclear studies are only beneficial as a screening test to direct angiography *(69)*, and some studies have failed to demonstrate any increase in the sensitivity of angiography when nuclear medicine studies were used *(38,70)*. Still other authors have found it to be a very poor screening tool and recommend that it has no place in the initial diagnostic workup of acute GI bleeding *(70–72)*.

When there is clinical suspicion that a Meckel's diverticulum might be the source of hemorrhage, then a Meckel's scan, using Tc99m-pertechnetate as the radiotracer, is the recommended diagnostic study. The diagnostic accuracy of a Meckel's scan is over 90% *(73)*. A Meckel's diverticulum is the persistence of the omphalomesenteric duct located

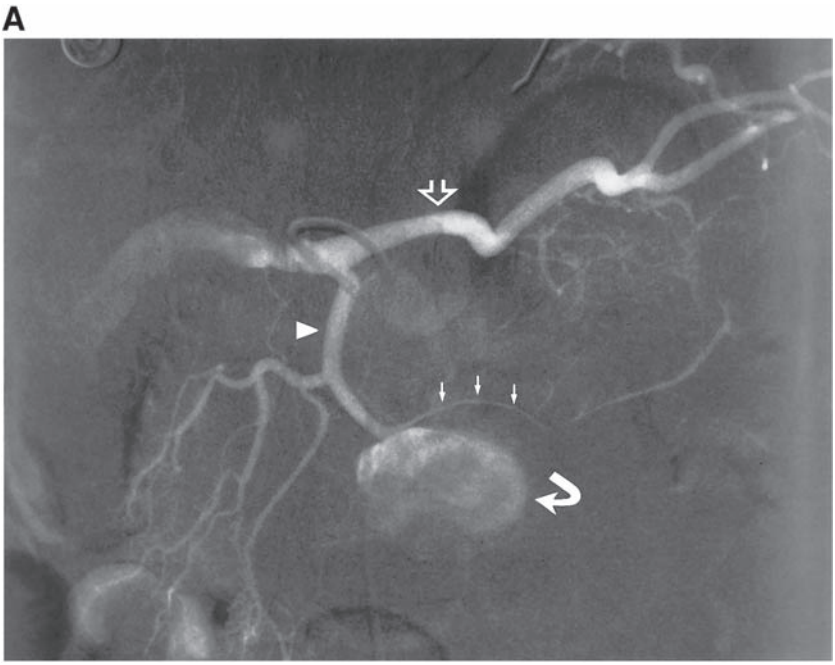

Fig. 9. Transcatheter embolization of a pancreatic pseudoaneurysm. **(A)** Selective dorsal pancreatic angiogram, in a patient with history of pancreatitis and upper GI hemorrhage. Splenic artery (open arrow), dorsal pancreatic artery (arrowhead), transverse pancreatic artery (three small arrows), and pseudoaneurysm (curved arrow).

in the distal ileum. Hemorrhage arises from ulcerations caused by the presence of ectopic gastric mucosa. The goblet cells within the ectopic gastric mucosa accumulate Tc99m-pertechnetate and allow its identification. Although most symptomatic patients present by 2 years of age, bleeding from a Meckel's diverticulum can first present during adulthood.

Angiography

First described by Nusbaum and Baum *(74)* in 1963, the principles of angiography in the diagnosis of GI bleeding have essentially remained unchanged for the past three decades. Examination of the GI tract requires angiography of the celiac trunk and superior and inferior mesenteric arteries. Information obtained from the patient's history and preangiographic testing will aid in tailoring the arteriogram, improve its diagnostic acumen, and limit the amount of contrast given. If an upper GI source of bleeding is suspected, then selective arteriography of the left gastric artery and/or gastroduodenal artery and pancreatoduodenal

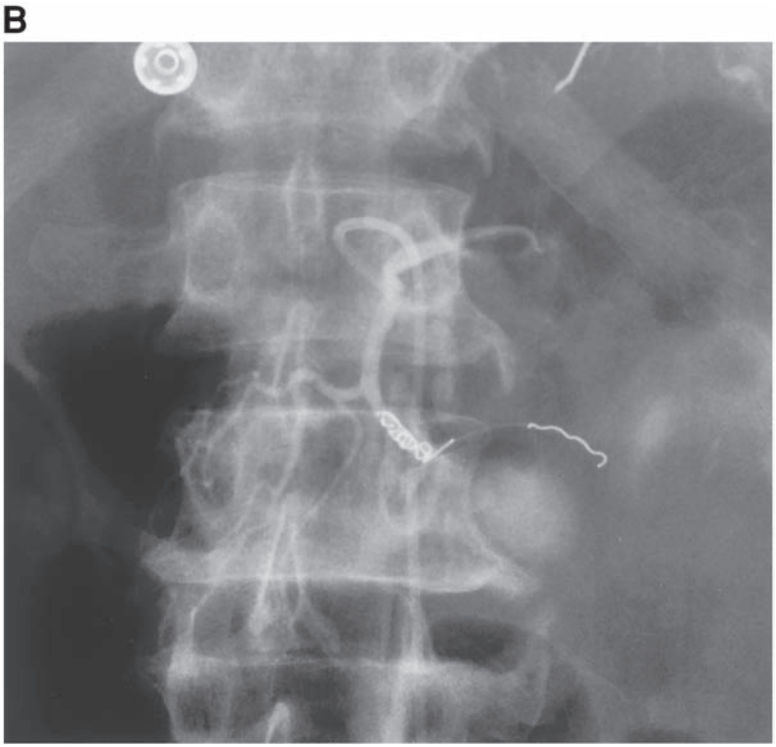

Fig. 9. *(continued)* **(B)** Embolic microcoils are deposited both distal and proximal to the pseudoaneurysm to prevent postembolotherapy recruitment of blood from the transverse pancreatic artery.

arcade may be necessary. Collateral branches from the inferior phrenic artery can supply a gastric or lower esophageal source of bleeding *(75)*. A lower GI bleed requires angiography of the inferior and superior mesenteric arteries, followed by the celiac trunk, if the first two studies prove negative. Occasionally, atypical feeding arteries from the splenic or left internal iliac artery will supply a colonic source of hemorrhage *(76)*.

Other forms of GI hemorrhage may not arise directly from the intestinal mucosa. Patients with a history of pancreatitis can present with bleeding from a pancreatic pseudocyst/aneurysm (Fig. 9) that has eroded into the bowel lumen or directly into the pancreatic duct (hemosuccus pancreatitis). A pancreatic pseudocyst/aneurysm is best identified on contrast-enhanced computed tomography (CT). A patient with GI bleeding following an abdominal intervention (i.e., percutaneous liver biopsy) should go directly to the angio suite to confirm the site of bleeding and have the source embolized (Fig. 10). Patients with a prior history of an

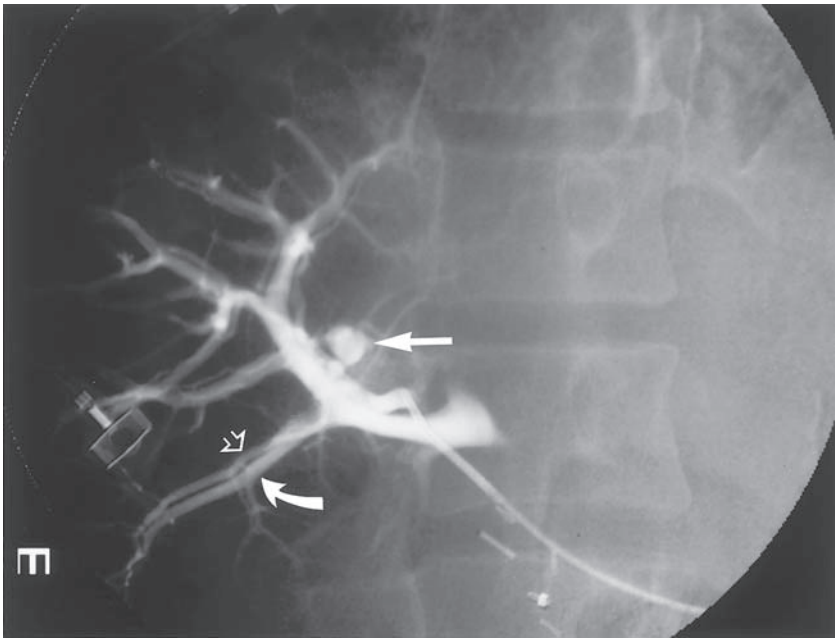

Fig. 10. Massive hemobilia following transjugular liver biopsy. Selective right hepatic angiogram, in a 43-year-old man who presented with upper GI bleeding from hemobilia following a transjugular liver biopsy, demonstrates a pseudoaneurysm (solid straight arrow) and an arterial venous fistula [hepatic artery (open arrow), portal vein (curved arrow)]. The hemorrhage ceased after the hepatic artery was embolized just proximal to the pseudoaneurysm.

abdominal aortic bypass graft and no other predisposing factors should have a contrast-enhanced CT examination to look for evidence of an aortoenteric fistula. If necessary, and if time permits, a preoperative biplane aortogram may follow.

In patients who are actively bleeding, arteriography should never be delayed, even in the presence of coagulation abnormalities. For angiography to be most sensitive, timing is critical. Angiography can detect bleeding as slow as 0.5 mL/min; however, the patient must be actively bleeding at the time contrast is injected into the blood vessel *(77)*. Prompt and early angiography has been shown to increase diagnostic accuracy significantly *(78,79)*. On the other hand, if the patient is hemodynamically stable and the bleeding appears to be intermittent in nature, then a nuclear medicine bleeding scan would be a better diagnostic choice. A positive bleeding scan can direct angiography (Fig. 8), and a negative study would make it reasonable not to subject the patient to an angiogram *(37,80)*.

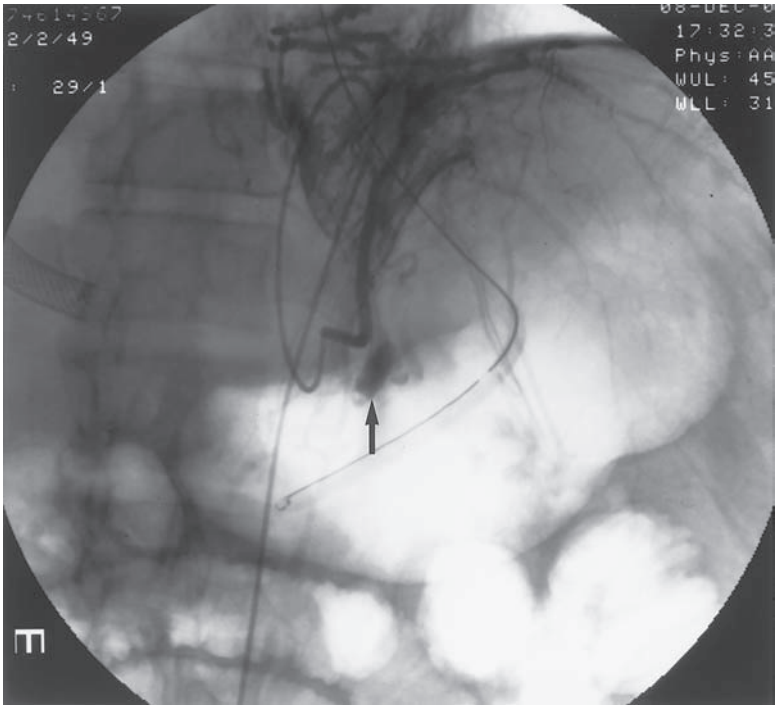

Fig. 11. Gastric hemorrhage simulated by left adrenal gland. Contrast staining of the left adrenal gland (arrow), during angiography of the left phrenic artery, can be confused with a bleeding gastric ulcer.

Although digital angiography lacks the spacial resolution of traditional cut film arteriography, digital studies are far superior with regard to contrast resolution, speed of obtaining and reviewing images, and ease of use. Digital arteriography allows the use of road mapping, which can assist the operator in directing the catheter into distal branch vessels. Many of the angiographic pitfalls to misdiagnosis (i.e., bowel hyperemia, adrenal gland staining) are common to both cut film and digital imaging *(81)* (Fig. 11). Unique to digital subtraction is the misregistration created by bowel gas and peristalsis, which may simulate an area of contrast extravasation (Fig. 12A). When in doubt, such areas of suspected hemorrhage should always be confirmed by reviewing nonsubtracted images.

The *sine qua non* of bleeding on an angiogram is the extravasation of iodinated contrast *(3)*. Extravasated contrast will collect along the dependent surface of the bowel lumen and persist well beyond the parenchymal and venous phases *(82)*. The collection of contrast may

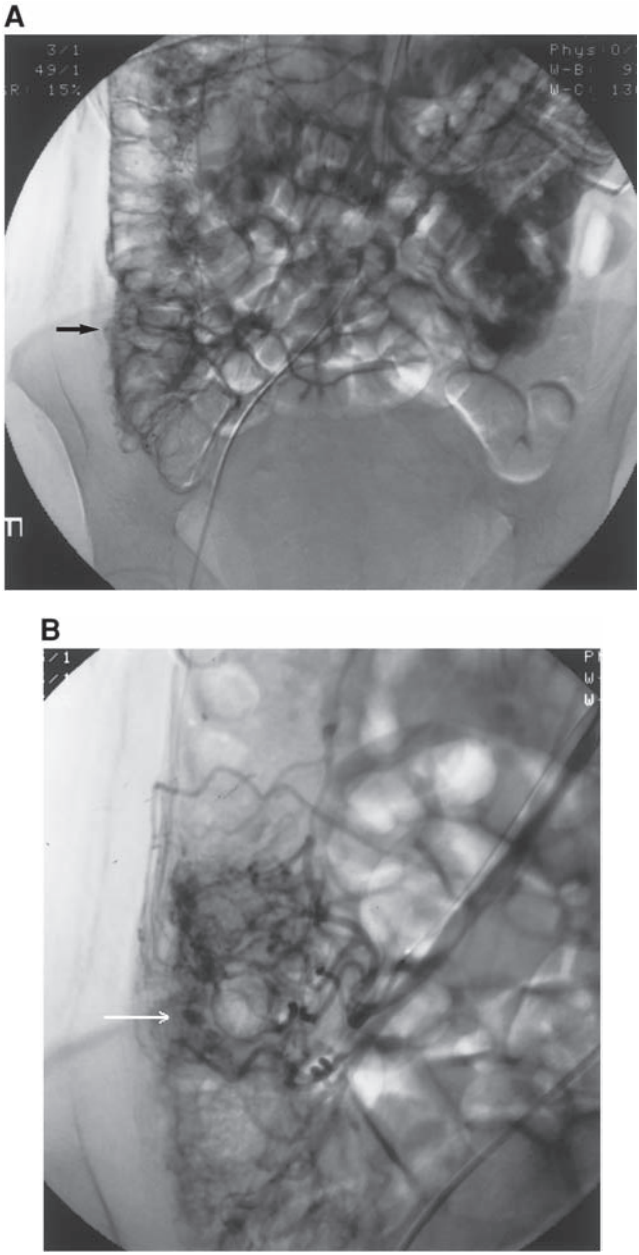

Fig. 12. Superselective polyvinyl alcohol (PVA) embolization of cecal hemorrhage. **(A)** Superior mesenteric angiogram, in a 58-year-old woman who presented with massive (24-U) lower GI hemorrhage, demonstrates extravasation (arrow) in the proximal ascending colon. Note the digital misregistration seen throughout abdomen caused by bowel peristalsis. Such artifacts can obscure or be mistaken for GI hemorrhage. **(B)** Selective arteriography through coaxial 3-Fr microcatheter defines area of hemorrhage (arrow).

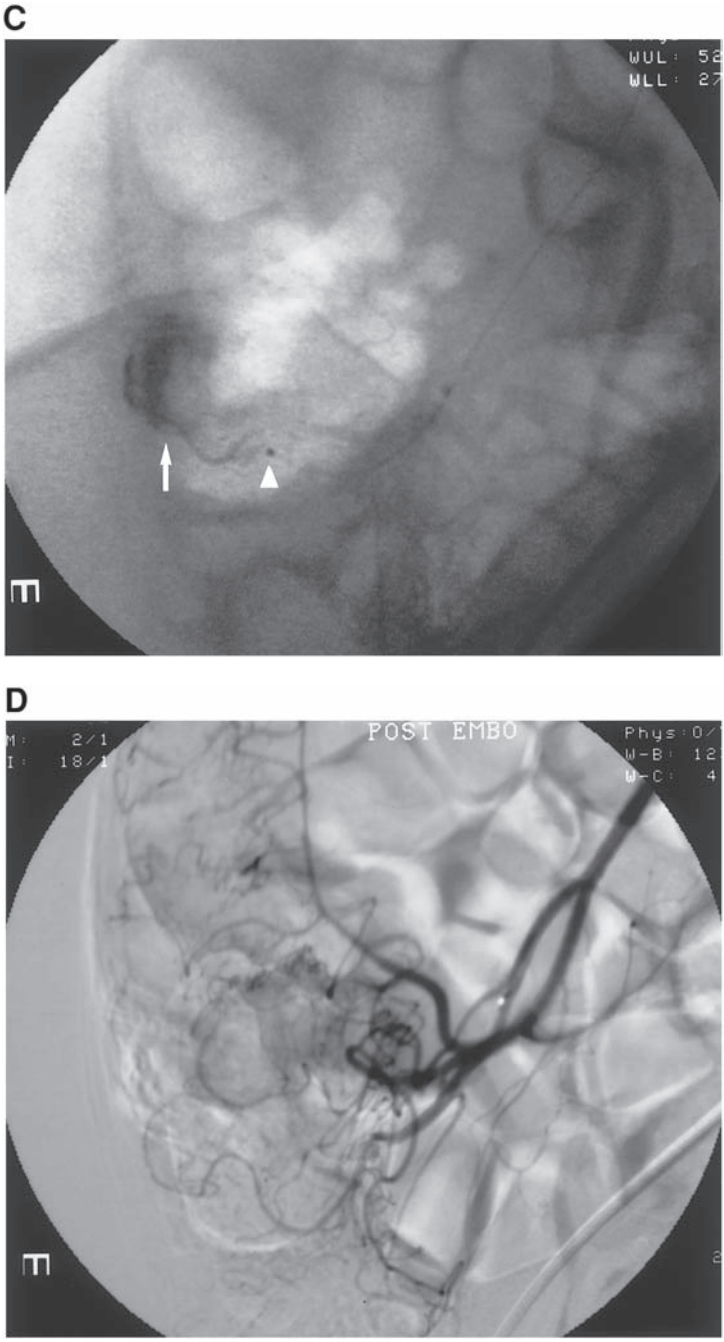

Fig. 12. *(continued)* **(C)** Bleeding was controlled after two tiny particles of PVA were injected through the 3-Fr microcatheter (arrowhead) placed just proximal to the bleed (arrow). **(D)** Postembolization arteriography documents no further evidence of bleeding.

localize between two bowel folds, giving the characteristic "pseudovein" sign that was first described by Ring et al. in 1973 *(83)*. With the exception of diverticular hemorrhage, aneurysms, and vascular tumors, most lesions responsible for GI hemorrhage will not demonstrate characteristic angiographic findings. Angiodysplasias (Fig. 5), although often quite subtle in appearance, are diagnosed by demonstrating early venous drainage, a vascular tuft, and/or delayed emptying of dilated intramural veins *(84)*. The angiographic appearance of a bleeding colonic diverticula (Fig. 4) can be diagnostic if one identifies contrast pooling within the diverticula before spilling over into the bowel lumen.

Variceal bleeding, in patients with cirrhosis and portal hypertension, is a common diagnostic problem for clinicians. Upper endoscopy should always precede angiography. In a large number of patients with portal hypertension and varices who present with GI bleeding, the source of the hemorrhage is a nonvariceal *(85)*. Most cases of active variceal hemorrhage will *not* be demonstrated by angiography. Arterial portography may, however, reveal signs of portal hypertension such as hepatopedal flow within the portal venous system and/or the presence of gastroesophageal varices (Fig. 2) *(86)*.

ENDOVASCULAR MANAGEMENT OF ACUTE GASTROINTESTINAL HEMORRHAGE

After the bleeding site has been identified, the medical team (internist, gastroenterologist, interventional radiologist, and surgeon) must decide on a treatment plan that will provide the safest and most effective solution. Depending on the suspected etiology of the bleed, the age and overall status of the patient, and the experience of the interventional radiologist, temporary or permanent transcatheter therapy may be offered. Transcatheter treatment consists of embolotherapy to occlude the arterial feeder supplying the hemorrhage or the infusion of a vasoconstrictive agent in an attempt to decrease the arterial flow and allow the patient's own coagulation process to seal the lesion. In patients with cirrhosis who are bleeding from gastroesophageal varices, the interventional radiologist can decrease elevated portal venous pressures by creating a transjugular intrahepatic portosystemic shunt (TIPS) between the portal and systemic venous systems.

Transcatheter Vasopressin

Vasopressin (Pitressin, Parke-Davis, Morris Plains, NJ) is a purified extract of the posterior pituitary hormone antidiuretic hormone. The use of catheter-directed, intraarterial infusion of vasopressin to control

Table 3
Complications of Pitressin (Vasopressin) Therapy for Gastrointestinal Hemorrhage

Ischemic heart disease
Mesenteric ischemia
Portal vein thrombosis
Acral cyanosis/digital gangrene
Hyponatremia
Cerebral edema

massive GI hemorrhage was first described by Baum et al. *(87)*. Vasopressin is a potent constrictor of smooth muscle. When it is delivered intraarterially, it reduces blood flow by stimulating contraction of the small and/or large bowel, as well as acting directly on the blood vessel wall. Vasopressin is infused directly through the diagnostic arterial catheter at a continuous rate of 0.2 U/min and increased up to 0.4 U/min when lower dosages are proved to be ineffective. Once bleeding has been shown to be under control, the infusion rate is maintained as the catheter is secured in position and the patient transferred to an intensive care unit for close observation. Follow-up arteriography is performed 12–24 hours after infusion is started. If at that time bleeding has discontinued, then the vasopressin infusion is slowly tapered over a 12–24-hour period to avoid rebound hyperemia *(21)*.

The overall success of vasopressin in controlling GI hemorrhage is between 65 and 85% *(21,78,87–90)*. Vasopressin has been shown to be highly effective in the control of gastric bleeding, especially diffuse hemorrhagic gastritis, achieving a reported success in 82% in this selected group *(91)*. In the control of *lower* GI hemorrhage, the success rate of vasopressin is between 47 and 92% *(88,92,93)*. Vasopressin appears to be very effective in controlling diverticular sources of bleeding but is less effective in stopping hemorrhage arising from angiodysplasias or neoplasias *(33,36)*. Rebleeding also carries a considerable morbidity and mortality, and studies have reported the incidence of recurrent diverticular hemorrhage (after initial successful control) to be as high as 40% *(21,33,88,90,92,94,95)*.

Not every patient is suitable for intraarterial vasopressin therapy, and ischemic heart disease is considered an absolute contraindication (Table 3). Treatment with vasopressin is associated with a 9% major complication rate. Complications such as mesenteric ischemia, bowel infarction, portal vein thrombosis, acral ischemia, hyponatremia, and cerebral edema have been described *(21,30)*.

Transcatheter Embolotherapy

Arterial embolization has been used with success in patients who have failed less invasive measures *(27,30,93,96–100)*. Compared with vasopressin, embolotherapy has the advantage of gaining immediate control of the bleeding, avoiding the complications of retaining a catheter within the mesenteric artery and the expense of prolonged hospitalization within the intensive care unit. In the event that the patient will ultimately go to surgery, preoperative transcatheter embolization can provide time for the replacement of lost blood products and the correction of any underlying coagulopathy.

The most common embolic material used is Gelfoam (Upjohn, Kalamazoo, MI), which is considered a temporary occluding agent. However, many different embolic agents have been used in the treatment of hemorrhage, including autologous blood clot, stainless steel coils, platinum microcoils, polyvinyl alcohol (PVA) particles, and even silk threads *(19,101–103)*. Small-particulate embolic material (Gelfoam powder, collagen suspensions) and liquids (absolute alcohol) should be avoided because they carry a high risk of bowel necrosis.

In the case of continued *upper* GI hemorrhage following failed endoscopic control, embolotherapy can provide immediate and definitive treatment. Since Rosch et al. *(104)* reported the successful transcatheter embolization of a bleeding right gastroepiploic artery with autologous blood clot in 1972, transcatheter embolotherapy has established itself as a safe and effective treatment modality in the control of *upper* GI bleeding (Fig. 1). In the case of severe hemorrhage arising from a gastric or duodenal source that was identified on endoscopy but failed angiographic localization, empiric embolization of the left gastric or gastroduodenal artery warrants consideration *(19)*.

In *lower* GI bleeding, the most important and feared complication (after transcatheter embolotherapy) is transmural infarction, with resultant bowel perforation. Based on a heavily cited report published in 1982 by Rosenkrantz et al. *(105)*, many interventional radiologists concurred that the use of embolotherapy to control *lower* GI hemorrhage carried too great of a risk of bowel infarction. In the study of Rosenkrantz et al. *(105)*, postembolic colonic infarction occurred in 3 of 23 patients, and most authors attributed this high rate of ischemia to the lack of effective collateral circulation unique to the small and large bowel. During the late 1970s and early 1980s, interventional radiologists were performing *sub*selective embolizations using 6- and 7-Fr catheters and injecting embolic material from a proximal second- or third-order branch vessel *(105–109)*. Embolizations were also fre-

quently performed immediately following a failed trial of vasopressin. Vasopressin, a potent vasoconstrictor, decreases important collateral blood flow that is necessary to avoid infarction within the bowel segment that is embolized.

In the past decade, interventional radiology has experienced major advances in catheter and guidewire technology allowing improved *super*selective catheterization of smaller, peripheral branch arteries using coaxial 2.5- and 3.0-Fr catheters (Fig. 12). Advances in digital angiography have allowed immediate viewing of images, improved contrast resolution, and digital road-mapping to guide catheter manipulation. These improvements in angiographic technique, contrast media, pharmacology, and embolic agents have greatly enhanced the safety and efficacy of embolotherapy *(110)*.

In 1992, Guy et al. *(101)*, *super*selectively placed coaxial microcatheters just proximal to the source of arterial bleeding and successfully controlled ten lower GI hemorrhages by embolizing 1–2 particles of PVA. Follow-up examination (colonoscopy, clinical evaluation) of the ten patients demonstrated no evidence of bowel infarction. Other investigators have produced similar results with *super*selective embolization using microcoils and/or PVA to control hemorrhage successfully in both the small (Fig. 13) and large bowel (Fig. 12) *(97–100)*.

Iatrogenic complications, following liver biopsy or percutaneous transhepatic cholangiography, can result in massive hemobilia (Fig. 10). Such intrahepatic sources of bleeding are difficult to manage surgically and are best treated with transcatheter embolotherapy *(19)*. In most cases of hemobilia, the source can be safely embolized without risk of hepatic necrosis if the portal vein is patent and demonstrates normal hepatopedal blood flow. In cases of hemobilia following percutaneous placement of a biliary drainage catheter, the initial hepatic angiogram may be negative if the indwelling catheter is intermittently tamponading the bleeding artery. A repeat study should then be performed after the catheter is removed over a wire.

Transjugular Intrahepatic Portosystemic Shunt

In the past two decades there have been significant advances in the management of patients with cirrhosis and portal hypertension. The availability of endoscopic sclerotherapy/banding, liver transplantation, and the TIPS procedure (Fig. 14B) has significantly improved the long-term outlook of these patients. Variceal bleeding occurs in one-third of patients with end-stage liver disease and carries a 30–50% mortality with every episode of hemorrhage. Upper GI endoscopy with injection

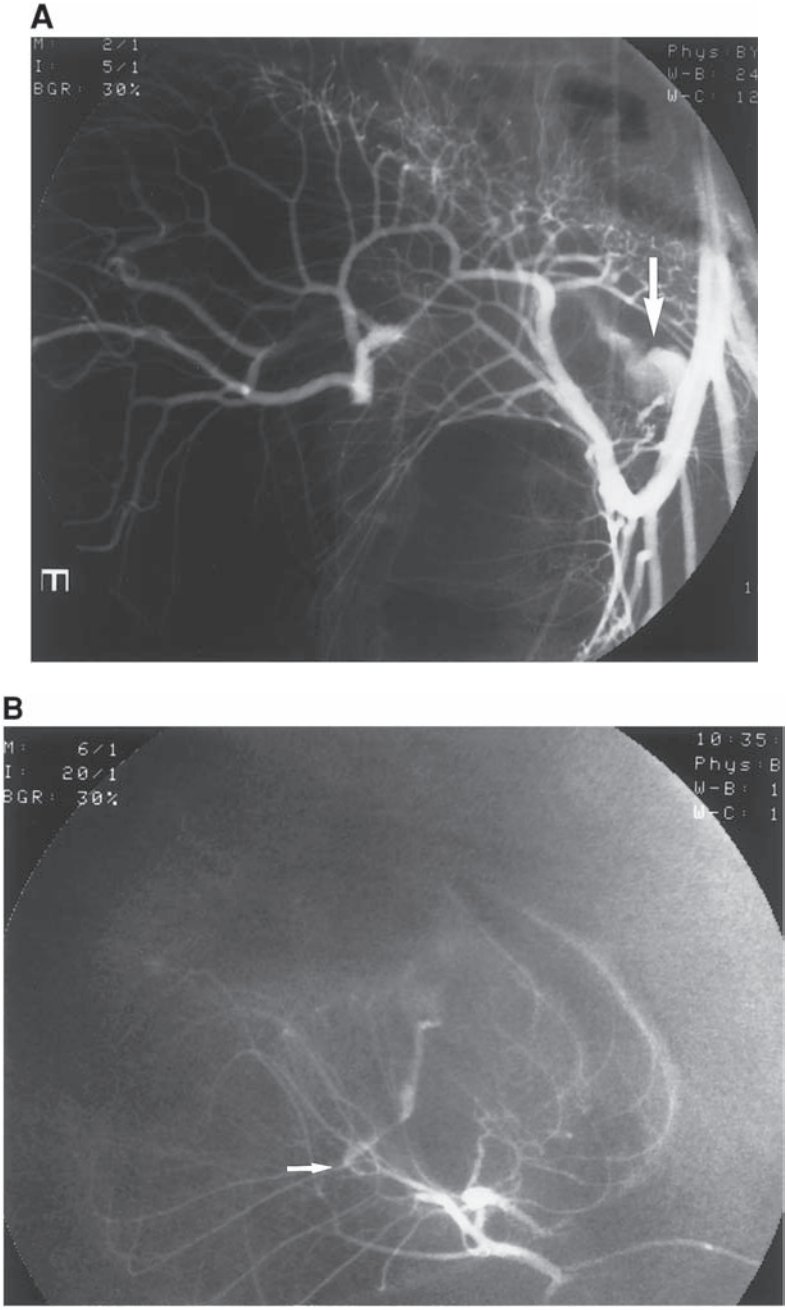

Fig. 13. Superselective microcoil embolization of small bowel hemorrhage. **(A)** Magnified view of a superior mesenteric angiogram from a 28-year-old man with massive lower GI hemorrhage. Contrast extravasation (arrow) is noted in the mid small bowel. **(B)** Angiogram from a 3-Fr coaxial microcatheter (arrowhead) positioned proximal to the bleeding source (arrow).

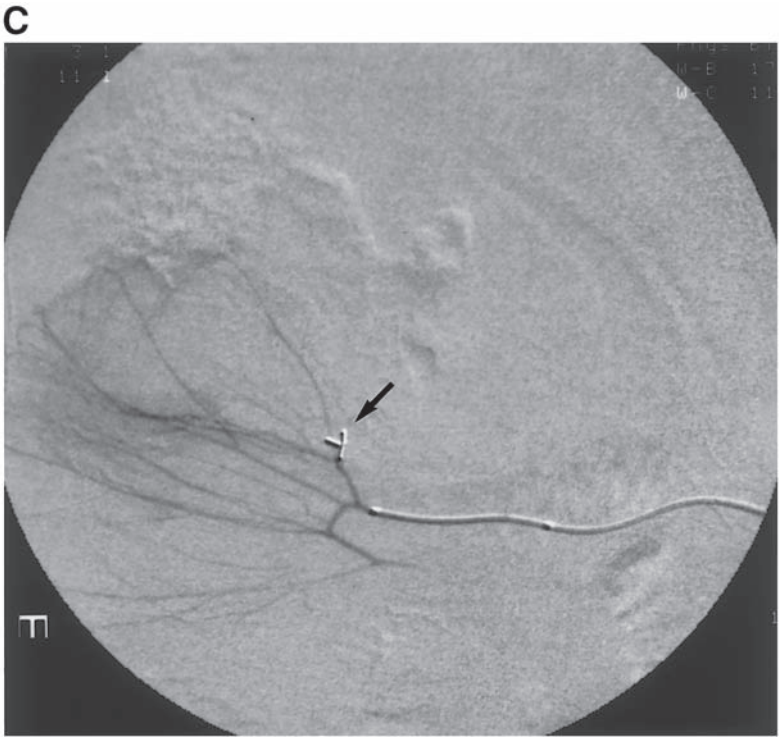

Fig. 13. *(continued)* **(C)** Postembolization angiogram shows no further hemorrhage following placement of two microcoils (arrow).

sclerotherapy and/or band ligation should be the initial diagnostic test and therapy *(111)*. Endoscopic management is successful in controlling bleeding in more than 90% of patients *(112)*. When endoscopy fails to control bleeding, the interventional radiologist should be summoned for decompression of the portal venous system by placement of a TIPS.

The TIPS procedure was first described in 1969 by Rosch et al. *(113)*. Today, it has evolved into a safe and effective procedure that is available at most medical centers where trained interventional radiologist practice. In most cases the procedure takes 1–2 hours to perform and can be carried out under deep conscious sedation. Compared with an emergent surgical shunt, which carries an operative mortality rate of up to 42% *(114)*, the procedure related mortality from the TIPS procedure is less than 2% *(115)*.

The Achilles' heel of the TIPS procedure is shunt malfunction, which occurs in 35–75% of patients within the first year *(116,117)*. Although most shunt restenoses can be easily revised as an outpatient procedure

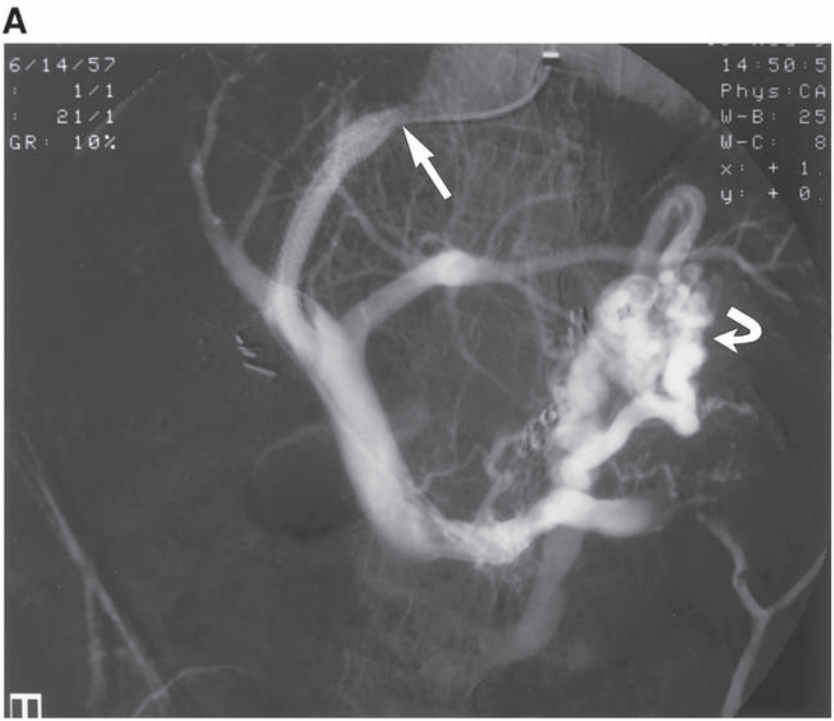

Fig. 14. TIPS stenosis and revision. **(A)** Direct portography in a 42-year-old man who presented with recurrent variceal hemorrhage 3 months after creation of a transjugular intrahepatic portosystemic shunt (TIPS). Direct measurement reveals an elevated portosystemic pressure gradient. Digital portography shows a distal shunt stenosis (straight arrow). Note the hepatofugal flow through a native splenorenal shunt that feeds large gastric varices (curved arrow).

with minimal risk to the patient, close surveillance is mandatory to avoid recurrent variceal bleeding. Patients who return with bleeding should have their TIPS immediately reevaluated in an angio suite, and any shunt stenosis or thrombosis should be revised with angioplasty and/or stenting (Fig. 14).

SUMMARY

GI bleeding can be a confusing clinical conundrum, and patients presenting with an acute hemorrhage are at risk of considerable morbidity and mortality. During initial hemodynamic stabilization, the clinician must devise an orderly approach that will expedite diagnosis and treatment. Consulting a team of medical specialists that includes the

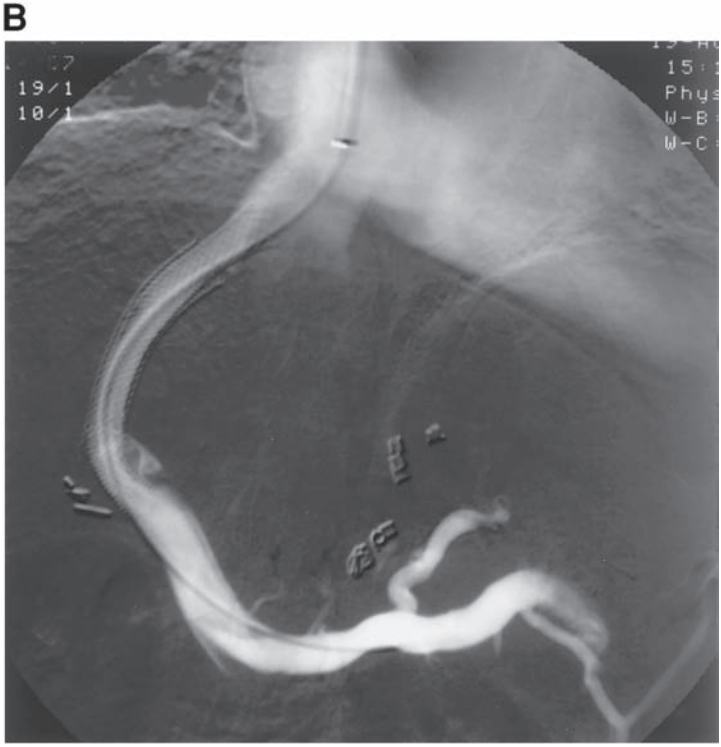

Fig. 14. *(continued)* **(B)** Following revision (angioplasty and stenting) of the intrahepatic shunt, the portosystemic pressure gradient decreased to the previous, post-TIPS level.

internist, gastrointerologist, surgeon, and interventional radiologist should provide the best possible management for the patient. Precise identification of the bleeding source is crucial, and the interventional radiologist can greatly assist in the diagnosis and sometimes the treatment. With the improvement in today's angiography equipment and advances in the subspecialty training of interventional radiology, clinicians can offer safer and superior diagnostic and therapeutic options to their patients.

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Acute Gastrointestinal Bleeding

Diagnosis and Treatment

Edited by

Karen E. Kim, MD

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Acute gastrointestinal (GI) bleeding accounts for over 300,000 hospitalizations per year and has high morbidity and mortality in those who go undiagnosed. In Dr. Karen Kim's *Acute Gastrointestinal Bleeding: Diagnosis and Treatment,* leading experts in the fields of gastroenterology, surgery, and radiology comprehensively review the pathophysiology, diagnosis, management, and treatment of acute bleeding disorders of the GI tract. The authors break down acute bleeding into upper and lower GI tract sources and provide a differential diagnosis for each disease, evidence-based algorithms for clinical practice, treatment modalities for its management, and standards of care. General approaches to the acute GI bleeding patient are discussed in terms of supportive care, early detection, and determination of upper vs lower GI bleed, when to transfuse, as well as early predictors of morbidity and mortality. The authors outline the many dilemmas faced by physicians in their approach to their patients, such as localization of the bleeding source (upper vs lower), the need and timing for emergency endoscopy, and the timing for radiologic intervention and/or surgery.

Authoritative and clinically focused, *Acute Gastrointestinal Bleeding: Diagnosis and Treatment* offers practicing clinicians—including primary care and emergency physicians, gastroenterologists, and those in clinical training—a comprehensive, up-to-date overview of this extremely common, and sometimes fatal, medical problem.

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