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Acute Nonvariceal Upper Gastrointestinal Bleeding: Endoscopic Diagnosis and Therapy

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Upper gastrointestinal bleeding (UGIB) is a relatively common, potentially life-threatening condition that causes more than 300,000 hospital admissions and about 30,000 deaths per annum in America [1]. Treating and preventing UGIB costs many billions of dollars per annum [2]. Endoscopic therapy has revolutionalized the treatment of UGIB, with a recently greatly expanded therapeutic armamentarium (Box 1). Clinicians—whether internists, gastroenterologists, intensivists, or gastrointestinal surgeons—have to become generally familiar with the new endoscopic therapies and their indications to form a knowledgeable and cohesive team to optimize patient care. This review of diagnostic and therapeutic esophagogastroduodenoscopy (EGD) for nonvariceal UGIB (NVUGIB) focuses on novel therapies and their indications, to optimize patient therapy and thereby decrease patient morbidity and mortality. The preceding article in this issue by the same authors discusses the initial management of acute UGIB before EGD, whereas the following article by Drs. Toubia and Sanyal reviews variceal UGIB.

Epidemiology

UGIB is defined as bleeding proximal to the ligament of Treitz, to differentiate it from lower gastrointestinal bleeding involving the colon, and middle gastrointestinal bleeding involving the small intestine distal to the ligament of Treitz [1]. The annual incidence of hospitalization for acute UGIB is 1 per 1000 people in America [3]. UGIB has a mortality of 7%

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Box 1. Endoscopic therapies

Injection therapy
Epinephrine with normal saline
Sclerotherapy
Thrombin
Fibrin sealant
Cyanoacrylate glue

Ablative therapy
Contact methods
- Thermocoagulation—heater probe
- Electrocoagulation—BICAP, traditional Gold probe, ERBE*
- Cryotherapy

Noncontact methods
- Photocoagulation—Nd:YAG laser
- Argon plasma coagulation (APC)

Mechanical therapy
Endoclips
Detachable snare—endoloop
Bands
Suturing device

Combined therapy devices
Probe combining electrocautery with needle injection
Device combining electrocautery with mechanical therapy

* ERBE Elektromedizin, Tubingen, Germany.
Abbreviations: BICAP, bipolar electrocoagulation probe; Nd:YAG, neodymium-doped yttrium aluminum garnet.

to 10% [4]. The mortality has decreased only minimally during the last 30 years, despite the introduction of endoscopic therapy that reduces the rebleeding rate. This phenomenon is attributed to the increasing percentage of UGIB occurring in the elderly, a group with a worse prognosis than other patients because of their increased use of antiplatelet medications or anticoagulants, and their frequent comorbid conditions [5,6]. Endoscopic therapy has, however, been shown to reduce the rate of rebleeding, the need for blood transfusions, and the need for surgery [1].

Endoscopy

EGD is the prime diagnostic and therapeutic tool for UGIB [7]. It accurately delineates the bleeding site and determines the specific cause. EGD is 90% to 95% diagnostic for acute UGIB [8]. Multiple clinical scoring systems

incorporate the endoscopic findings with clinical parameters on admission, including time from onset of bleeding to hospitalization, hemodynamic status, bleeding presentation, hematocrit, nasogastric tube aspirate findings, and patient comorbidities [9–11]. These scoring systems are valuable for prognostication and triage of patients who have NVUGIB [9,10]. Older age, hematochezia, shock, and a spurting artery or visible vessel at EGD are consistently negative prognostic factors, as is UGIB in patients already hospitalized for another cause [9,12]. For UGIB from peptic ulcer disease (PUD), the endoscopic findings by themselves are valuable predictors of the risk for rebleeding, need for blood transfusions, need for surgery, length of hospital stay, and mortality (Box 2) [13,14]. These prognostic data provide a rational basis for triage of patients to an unmonitored bed versus the ICU. Endoscopic parameters are also used in clinical trials to evaluate the efficacy of pharmacotherapy.

A multidisciplinary team approach, in conjunction with scoring systems that incorporate the endoscopic findings, reduces the hospital length of stay and thereby reduces hospital costs without adversely affecting patient outcome [13,15,16]. Patients who have a low clinical score, indicating a low risk for rebleeding, might conceivably be discharged immediately after EGD, but this strategy is generally not practiced [17,18]. Our practice is to perform EGD before discharge on all patients who have acute UGIB, and to admit all such patients if the EGD confirms a UGIB. Likewise, patients in the ICU who have low-risk endoscopic findings or successful endoscopic hemostasis may be triaged to a regular hospital bed [8].

The efficacy of endoscopic therapies for UGIB is assessed in clinical trials by the rebleeding rate, blood transfusion requirements, need for repeat EGD, need for surgery or angiography, length of hospital stay, medical costs, and mortality, including 30 day mortality, in-hospital mortality, or UGIB-related mortality.

Consent

The endoscopist should briefly describe to the patient the procedure technique, risks, benefits, and alternatives and obtain written, signed,

Box 2. Endoscopic findings in peptic ulcer disease as predictors of rebleeding

Endoscopic finding and rebleeding rate within 72 hours
Spurting artery, 90%–100%
Actively oozing blood, 80%
Visible vessel, 40%–60%
Adherent clot, 20%–25%
Flat pigmented spots on ulcer, 13%
Clean ulcer base, 5%

and witnessed informed consent. The consent should include contemplated endoscopic therapies. If the patient is obtunded or mentally incompetent, consent is obtained from the next of kin or legal guardian. Emergency administrative consent is obtained, as per written hospital protocols, when EGD is emergently required and the next of kin is unavailable. Patients who refuse cardiac resuscitation or endotracheal intubation ("do not resuscitate" status) can still undergo EGD if appropriate consent is obtained. Our policy is to require the patient or the next of kin to waive these treatment restrictions during the EGD to handle endoscopic emergencies.

Anesthesia

Attendance of an anesthesiologist at EGD is currently decided arbitrarily by the endoscopist's preference, anesthesiologist's availability, and patient's wishes. Use of an anesthesiologist, a costly resource, should be allocated according to rational criteria, as proposed in Box 3. A separate consent for anesthesiology is obtained if an anesthesiologist attends the EGD. The patient should be informed of the potentially greater medical costs if an anesthesiologist is used.

EGD is generally performed with a combination of a narcotic, either fentanyl or meperidine, and a benzodiazepine, either midazolam or diazepam, administered by the gastroenterologist. EGD is increasingly performed using propofol for deeper sedation and faster recovery. The deeper sedation is advantageous in highly anxious patients, patients who have psychiatric disorders, patients who have previously not tolerated EGD, and intravenous

Box 3. Reasonable indications for an anesthesiologist at esophagogastroduodenoscopy

Patient highly unstable from severe acute gastrointestinal bleeding
American Society of Anesthesiologists class III or IV patient: mild-moderate gastrointestinal bleeding in a patient who has comorbid conditions
Patient receiving mechanically assisted ventilation
Severely unstable vital signs (regardless of cause)
Highly uncooperative patient
Active recent substance or alcohol abuse
Advanced cirrhosis/liver failure
Planned sclerotherapy or banding from gastroesophageal varices
History of failed attempts at esophagogastroduodenoscopy (EGD) without anesthesiology assistance

drug abusers or alcoholics who tend to be difficult to sedate; it is advantageous in complex, prolonged procedures, such as banding of bleeding esophageal varices. The faster recovery streamlines turnover of outpatients because of shorter postprocedural monitoring.

Although traditionally administered by anesthesiologists because of the risk of respiratory depression, propofol is increasingly being administered by gastroenterologists and nurses, without anesthesiologists, with high efficacy and safety [19,20]. Nurses, under the supervision of a gastroenterologist, safely administered propofol in 36,743 endoscopic procedures with no cases requiring endotracheal intubation or resulting in death, neurologic sequelae, or other permanent injury [21]. For patient safety, the propofol dosage is titrated at EGD to a moderate level of sedation and the patient is carefully monitored for respiratory depression [22].

Endoscopy equipment and setting

A large-caliber, dual-channel, therapeutic endoscope, with one channel for water lavage or suction and a second channel for insertion of therapeutic catheters, is preferred for acute UGIB. A water pump is useful to vigorously and extensively lavage blood and clots to visualize underlying lesions. At a minimum, a sclerotherapy needle for epinephrine injection and another means of therapeutic endoscopy should be available at the bedside for NVUGIB, and esophageal banding should be available for variceal UGIB. The endoscopist should test all ports, buttons, and dials on the endoscope head before the EGD to verify that they function properly. A trained assistant should be in attendance at EGD to monitor the patient's vital signs and level of consciousness and to assist in therapeutic endoscopy. For the convenience of endoscopy staff, Boxes 4 and 5 provide checklists for the patient and equipment conditions necessary for EGD.

EGD for acute UGIB should be performed in a hospital, not a freestanding ambulatory surgical center. EGD is best performed in the hospital endoscopy suite, where the required equipment and trained staff are available. Patients who have exsanguinating hemorrhage, highly unstable vital signs, or severe comorbidities may be too unstable to be transported to the endoscopy suite. In such cases, emergency EGD is performed at the bedside in a monitored unit, such as the emergency room, operating room, or ICU.

Esophagogastroduodenoscopy risks

EGD rarely causes serious complications, such as gastrointestinal perforation, precipitation of gastrointestinal bleeding, aspiration pneumonia, respiratory arrest, cardiovascular complications, and missed lesions [23]. The benefit of EGD must be weighed against these risks in high-risk patients, such as those who have acute myocardial infarction [24–26].

Box 4. Checklist for esophagogastroduodenoscopy for acute upper gastrointestinal bleeding: patient status

- Valid EGD consent
  - Type of consent
    - Written
    - Informed
    - Includes contemplated endoscopic therapies
  - Conscious patient
    - From patient
  - Unconscious patient
    - Closest relative
    - Legal guardian
  - Administrative consent in emergency
  - Separate consent for anesthesiology if anesthesiologist in attendance
- Patient stability
  - Vital signs stabilized if possible with patient resuscitation
    - If cannot stabilize vital signs, consider EGD only if emergently indicated
  - Severe coagulopathy corrected
  - Severe electrolyte disorders corrected
  - Adequate volume resuscitation
  - Respiratory status stabilized
    - May require supplemental oxygenation
    - May require endotracheal intubation
- Secure, well-functioning, wide-bore intravenous lines in place
- Nothing per os
- Allergies checked—not allergic to contemplated endoscopic medications
- Stomach cleared
  - Nasogastric aspiration
  - Or intravenous erythromycin

Urgent esophagogastroduodenoscopy

Urgent EGD for NVUGIB is ideal, but significantly improves the clinical outcome over routine EGD only in special circumstances requiring urgent endoscopic hemostasis, such as severe, ongoing hemorrhage or esophageal variceal hemorrhage [27]. Early EGD may not diminish the mortality in other circumstances [28]. Early EGD helps identify stigmata of recent hemorrhage (SRH), which often disappear quickly after bleeding cessation [29]. Identification of SRH helps to determine which lesion bled when more than one lesion is identified at EGD. For example, a patient who has

Box 5. Checklist for esophagogastroduodenoscopy for acute upper gastrointestinal bleeding: equipment status

Endoscopic equipment
Double-channel therapeutic esophagogastroduodenoscope
Endoscope tested: all ports and buttons properly functioning
Endoscopic therapy
- Heater probe, BICAP, Gold probe, or APC available
- Dilute epinephrine available
- Sclerotherapy needles available
- Banding equipment or sclerosant available to treat esophageal varices
- Adequate water pump available
- Trained endoscopy nurse available for assistance

Other equipment
Emergency (crash) cart
- Fully equipped with medications for cardiac resuscitation
- Electrical cardiac defibrillator machine
- Equipment for endotracheal intubation and for manual mechanical respiration

Abbreviations: BICAP, bipolar electrocoagulation probe; APC, argon plasma coagulation.

two ulcers of equal size likely bled from the ulcer exhibiting more severe SRH. Identification of high-risk SRH permits early endoscopic intervention to reduce the risk for rebleeding.

Prompt EGD is often unattainable [30,31]. A large multicenter study reported a mean time of 12 hours from presentation with UGIB to EGD because of obstacles, including patient presentation during off-hours, lack of on-call nurses, or patient comorbidities, such as chest pain, that required evaluation before EGD [32]. Inpatients have worse clinical outcomes than outpatients who have acute UGIB despite a shorter mean endoscopy waiting time. Greater endoscopist experience is an independent factor that improves the outcome for NVUGIB [33].

Peptic ulcer disease

At EGD, ulcers appear as depressed craters, in contrast to erosions that lack depth. Pathologically, an ulcer penetrates through the muscularis mucosa into the submucosa. At EGD, ulcers are characterized by size, number, location, acuity, and SRH. Acute ulcers exhibit fibrinopurulent exudation, erythema, an inhomogeneous base, and edema, whereas chronic ulcers exhibit fibrosis, scarring, a homogeneous base, and partial healing.

Duodenal ulcers are rarely malignant, whereas 5% of gastric ulcers are malignant [34]. Gastric ulcers are classified at EGD as likely benign as evidenced by a round margin, smooth border, antral or prepyloric location, small size, radiating folds, and lack of an associated mass. Gastric ulcers are classified as likely malignant as evidenced by an irregular and indurated border, heaped-up margins, proximal gastric location, large size, absence of gastric folds near the ulcer, and an associated mass. Gastric ulcers are classified as indeterminate if they have ambiguous features. At EGD numerous biopsies should be taken at the margin of a gastric ulcer to exclude malignancy. Performance of at least seven biopsies from the ulcer margin and base, together with the endoscopic appearance, is 98% sensitive at diagnosing malignancy [35]. These biopsies may be deferred at an initial EGD when the ulcer is actively bleeding or has recently bled to avoid exacerbating or inducing bleeding. Gastric ulcers are generally followed by repeat EGD to document healing to exclude a nonhealing malignant ulcer [36].

Up to 80% of duodenal ulcers are caused by *Helicobacter pylori* infection, whereas about 50% of gastric ulcers are associated with this infection [37]. The prevalence of *H pylori* infection in duodenal ulcers has, however, been recently decreasing in America because of increasing administration of antibiotics in general or as specific therapy for chronic *H pylori* infection [38]. About 15% of patients who have *H pylori* infection develop duodenal ulcers. The virulent bacterial strain that contains the *cagA* gene is strongly associated with duodenal ulcers [39]. Patients who have PUD should undergo endoscopic biopsies of the antrum to test for this infection. Patients who have PUD and documented infection should receive triple therapy, including antibiotics and acid suppressive therapy, to eradicate this infection. Eradication induces ulcer healing and helps prevent ulcer recurrence [40].

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute the most important cause of PUD after *H pylori* infection. All patients who have PUD should be carefully questioned about NSAID use. Patients frequently do not report NSAID use because NSAIDs are perceived as minor painkillers and are often taken without a prescription [41]. Wilcox and colleagues [42] reported that 65% of patients who had UGIB were taking aspirin or other NSAIDs, often administered without a prescription. Although NSAIDs can cause duodenal ulcers, they most commonly produce antral ulcers [43]. They are an especially common cause of PUD in the elderly [41].

About half of NSAID-induced ulcers are painless because of the analgesic properties of NSAIDs that can mask the pain of ulcers and the early discontinuation of NSAID therapy (before developing PUD) in patients who experience abdominal pain [41]. Endoscopic biopsies are safe in patients taking aspirin or other NSAIDs, with a small increased risk of minor, clinically insignificant bleeding [44]. NSAID-induced ulcers often lack inflammation beyond the ulcer margin, whereas *H pylori*–induced ulcers usually occur in a background of chronic active gastritis [43]. NSAID-induced ulcers are treated by NSAID discontinuation or substitution of a less gastrotoxic alternative medication,

discontinuation of other gastrotoxic medications, treatment of concomitant *H pylori* infection if present, and proton pump inhibitor (PPI) therapy.

The Zollinger-Ellison syndrome (gastrinoma) should be considered in the differential whenever ulcers are multiple, refractory to conventional therapy, located in otherwise unusual places (such as the second portion of the duodenum or the esophagus), associated with thickened gastric folds, associated with an acidic diarrhea, or associated with gastric hypersecretion and hyperchlorhydria [45]. The Zollinger-Ellison syndrome is diagnosed by a highly elevated fasting serum gastrin level, in the absence of pernicious anemia, atrophic gastritis, histamine-2 receptor antagonist therapy, or PPI therapy [46]. A secretin test is useful when the gastrin level is only moderately elevated. In the Zollinger-Ellison syndrome, the serum gastrin level pathologically increases by at least 200 units after secretin administration [47].

Endoscopic therapy

About 25% of EGDs performed for UGIB incorporate endoscopic therapy [48]. UGIB usually ceases with conservative measures, but severe cases, with endoscopic SRH, require endoscopic therapy to achieve hemostasis and prevent rebleeding [49]. Without endoscopic therapy, PUD with SRH has a high incidence of rebleeding or continued bleeding (see Box 2). SRHs that require endoscopic therapy include active bleeding from an ulcer, whether severe or oozing, and a visible vessel, which refers to an elevated pigmented spot within an ulcer crater that may be red, purple, black, or gray (Fig. 1). An ulcer with a visible vessel has a high risk of rebleeding. Visible vessels that are prominently elevated or peripherally located within an ulcer base have a particularly high risk for rebleeding without endoscopic therapy [50]. Ulcers with a clean base or with a flat pigmented spot have a low risk of rebleeding and do not require endoscopic therapy. An algorithm describing which ulcers require endoscopic therapy is provided in Fig. 2.

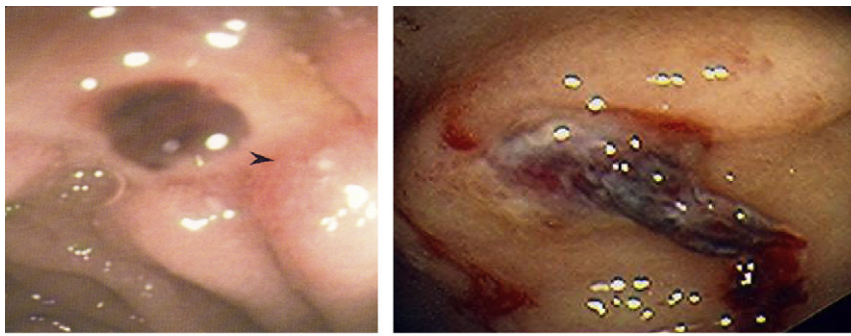
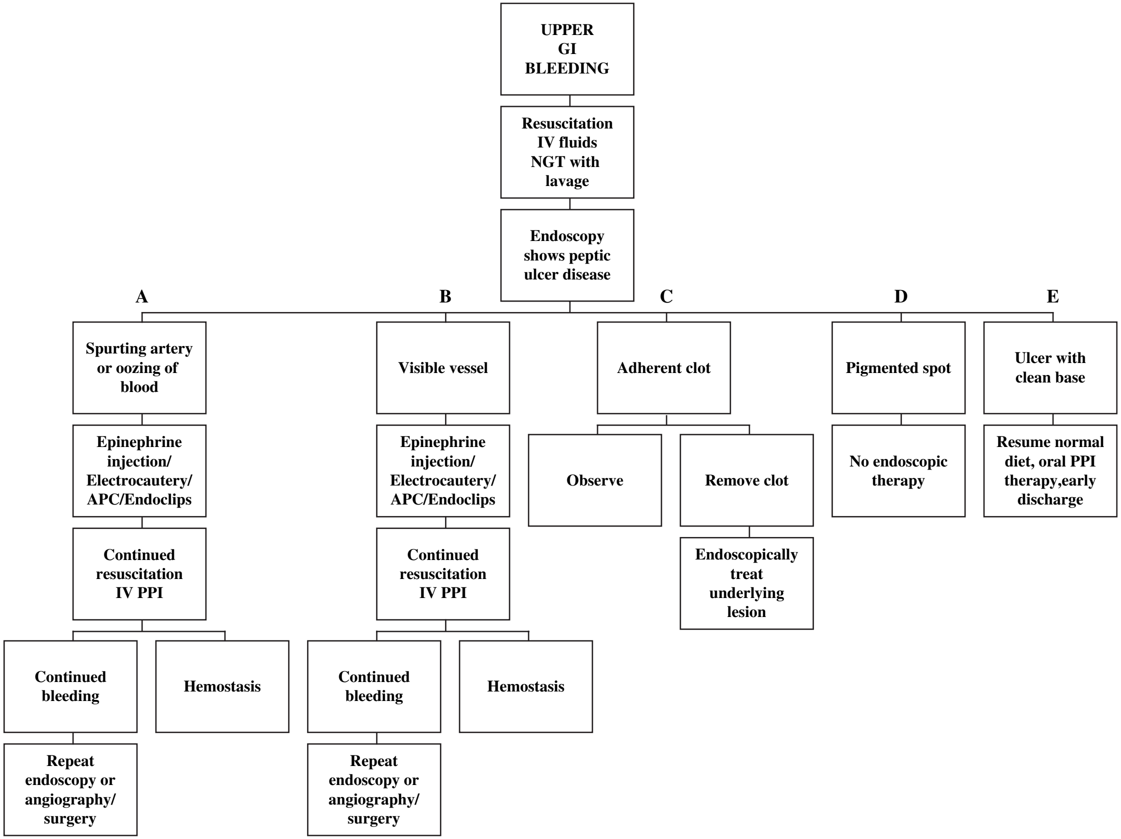


Fig. 1. (*Left*) Endoscopic videophotograph of a prominent red elevation within an ulcer that represents a visible vessel. (*Right*) Endoscopic videophotograph of an ulcer that contains a prominent dark red elevation, representing a visible vessel, with an attached clot.


UPPER GI BLEEDING
Resuscitation IV fluids NGT with lavage
Endoscopy shows peptic ulcer disease
A
B
C
D
E
Spurting artery or oozing of blood
Epinephrine injection/ Electrocautery/ APC/Endoclips
Continued resuscitation IV PPI
Continued bleeding
Hemostasis
Repeat endoscopy or angiography/ surgery
Visible vessel
Epinephrine injection/ Electrocautery/ APC/Endoclips
Continued resuscitation IV PPI
Continued bleeding
Hemostasis
Repeat endoscopy or angiography/ surgery
Adherent clot
Observe
Remove clot
Endoscopically treat underlying lesion
Pigmented spot
No endoscopic therapy
Ulcer with clean base
Resume normal diet, oral PPI therapy,early discharge

Pooled blood partly obscuring gastrointestinal lesions should be lavaged to avoid missing high-risk SRH. It is controversial, however, whether to remove a clot attached to an ulcer with vigorous lavage or cold guillotine by way of a snare for immediate endoscopic therapy if SRH are thereby exposed. Recent data suggest such aggressive therapy can diminish the risk for rebleeding [51,52], but does not diminish the need for surgery or reduce the mortality [53]. Many endoscopists avoid clot manipulation and medically treat such an ulcer with PPI therapy to stabilize the clot and promote hemostasis [54,55].

Unfavorable peptic ulcer locations increase the risk of rebleeding because of proximity to major vessels and reduce the efficacy of endoscopic therapy because of difficult endoscopic access [56]. Unfavorable locations include the proximal lesser curvature that overlies the lesser gastric artery, and the posterior duodenal bulb that overlies the gastroduodenal artery. Large (>2 cm wide) and deep ulcers also pose a greater risk of rebleeding [57]. The requirement for endoscopic therapy is, however, determined by endoscopic SRH rather than ulcer location or size.

Endoscopic therapies include injection, ablation, and mechanical therapy (see Box 1). All three therapies are effective as monotherapies, but combined therapies increase the efficacy. Treatment of UGIB has shifted from the operating room to the endoscopy suite. Ulcers with a visible vessel have a 40% to 60% rate of rebleeding and a 35% rate of requiring surgery without endoscopic therapy that is reduced to a 5% to 15% rate of rebleeding and a 5% to 10% rate of requiring surgery after endoscopic therapy [58]. Likewise, actively bleeding ulcers have about a 90% rate of continued or subsequent bleeding if untreated, which is reduced to a 10% to 15% risk of rebleeding after endoscopic therapy (see Box 2).

Injection therapy

Injection therapy for hemostasis is used for bleeding from PUD, Mallory-Weiss tears, and Dieulafoy lesions, and for bleeding after endoscopic

Fig. 2. Algorithm for endoscopic therapy of peptic ulcer disease. At endoscopy, the following ulcer characteristics determine the endoscopic therapy: (*A*) Spurting or oozing artery requires endoscopic therapy, such as epinephrine injection, thermocoagulation, APC, or endoclips, to promote hemostasis. If the attempted endoscopic hemostasis fails, the endoscopy is repeated to reapply the endoscopic therapy or the patient undergoes angiography or surgery for hemostasis. (*B*) A visible vessel within an ulcer is treated at endoscopy just like a spurting artery because of a high risk for rebleeding without therapy. (*C*) An adherent clot may be treated conservatively with PPI therapy without disrupting the clot, or may be treated aggressively by deliberate clot removal (either by vigorous lavage or guillotining the clot using a snare) followed by endoscopic therapy of the underlying lesion. Both approaches are currently considered the standard of care for an adherent clot. (*D*) Pigmented (flat) spot within an ulcer should not receive endoscopic therapy because of a low risk of rebleeding. (*E*) An ulcer with a clean base should also not receive endoscopic therapy because of a very low risk of rebleeding. A patient who has this finding can quickly resume a normal diet and be considered for early discharge. APC, argon plasma coagulation; GI, gastrointestinal; IV, intravenous; NGT, nasogastric tube; PPI, proton pump inhibitor.

polypectomy, endoscopic mucosal resection (EMR), or sphincterotomy. The assistant projects the needle, originally designed for variceal sclerotherapy, about 5 mm beyond the plastic sheath, injects the solution, and provides feedback regarding resistance during injection. No resistance suggests off-target injection. Multiple injections are applied around an ulcer and then directly at the bleeding point or visible vessel within the ulcer. Alternatively, some endoscopists initially target the bleeding site [59].

Epinephrine, at a concentration of 1:10,000, is the injection agent of choice in the United States. It is effective for hemostasis [60,61]. Epinephrine injection induces hemostasis by vasoconstriction, tamponade, and platelet aggregation [62]. Large volumes (>12 mL) are more effective than small volumes, but they might theoretically produce cardiovascular toxicity because of elevated serum epinephrine levels that last for 20 minutes after injection [63–65]. Epinephrine is not recommended as monotherapy because about 20% of patients rebleed after epinephrine injection alone [48,49]. It is often used to clear the endoscopic field before ablative or mechanical therapy. Risk factors for failure of this therapy include active bleeding, large ulcers, proximal gastric ulcers, posterior duodenal bulb ulcers, or significant coagulopathy [57,66].

Some endoscopists inject sclerosants, including sodium tetradecyl sulfate, polidocanol, or ethanol. Sclerosants cause greater vascular thrombosis than epinephrine, but induce greater tissue inflammation and injury that can cause iatrogenic ulcers or strictures. This potential for injury limits the amount of sclerosant that can be injected. Sclerosants are not combined with epinephrine injection because of an increased risk of tissue injury, without improved hemostatic efficacy [67].

Biologic glues are rarely used as injection therapy because of limited efficacy, cost, cumbersomeness, and potential toxicity. Thrombin initiates the clotting sequence and may promote ulcer healing. It is primarily an adjunctive agent. There are few clinical trials of thrombin for NVUGIB [68,69]. Fibrin sealant consists of thrombin and fibrinogen, which are combined at the needle tip in a dual-channel injection apparatus. Use of fibrin sealant does not add efficacy to the use of epinephrine alone [70]. There are numerous case reports of cyanoacrylate glue injection for gastric varices, and this glue has been used as salvage therapy after failure of traditional hemostasis. It can, however, cause pulmonary emboli [71,72].

Ablative therapy

Ablative therapy includes contact methods, such as the heater probe and electrocautery with the BICAP (bipolar electrocoagulation probe) or Gold probe, and noncontact methods (Fig. 3) [48,56]. Electrocautery devices are standardly bipolar to produce focal injury from a well-localized electrical circuit. Monopolar electrocautery is used only as salvage therapy if standard endoscopic therapies fail because it produces more diffuse injury from

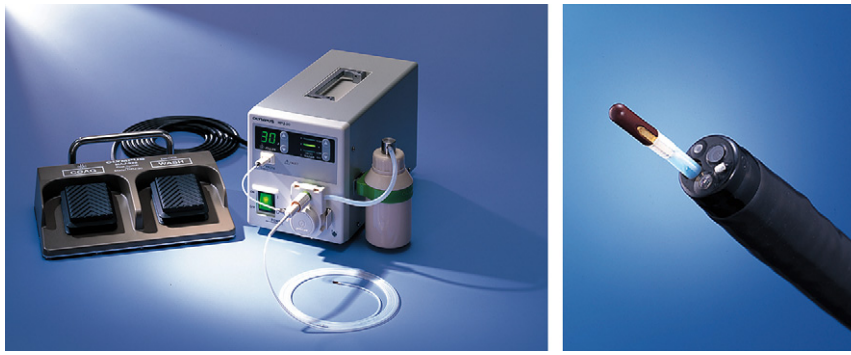


Fig. 3. Heater probe. Left photograph shows the entire heater probe apparatus, including the machine, attached water bottle for vigorous irrigation of lesions, foot pads for controlling the water irrigation, catheter (coiled plastic tube attached to the front of the machine), and wound up electrical cord. Right photograph shows a close-up view of the heater probe catheter tip extending 2 cm beyond the therapeutic channel of an endoscope. (*Courtesy of* Olympus America, Inc., Center Valley, PA; with permission.)

a poorly localized electrical circuit [73]. Bipolar electrodes complete the electrical circuit when the probe contacts the tissue [74]. The Gold probe (Microvasive Corporation, Milford, Massachusetts) has alternating spiral electrodes that form a bipolar electrode. Contact methods use coaptive coagulation, wherein the endoscopist forcefully presses the probe on the lesion while delivering electrical current and generating heat to compress, fuse, and seal the open wall of a bleeding vessel, much like a welder who applies pressure to fuse two pieces of metal together (Fig. 4). A large (3.2 mm wide) probe is applied at a low power setting for several seconds, with multiple applications, as necessary [74].

Argon plasma coagulation (APC) has supplanted the Nd:YAG laser as the noncontact ablative modality of choice for NVUGIB because of superior efficacy, greater portability, easier application, and lower cost [58,75,76]. APC produces more superficial tissue injury than the Nd:YAG laser and causes less frequent complications from deep tissue injury, such as a transmural burn or gastrointestinal perforation. APC can be used to treat (“paint”) diffuse, extensive lesions, such as the watermelon stomach (Fig. 5), whereas contact therapies are designed to treat point sources of bleeding [48,76].

APC, heater probe, and BICAP electrocautery have comparable efficacy for NVUGIB [48,58,77]. Use is dictated by personal experience, training, preference, cost, and availability. Ablative therapy diminishes the need for blood transfusions, decreases the need for surgery, and decreases morbidity, but has not been demonstrated to decrease mortality [56,74]. There is a low ($<1\%$) complication rate of iatrogenically induced ulcer bleeding or gastrointestinal perforation [74]. Ablative therapy is about as effective as epinephrine injection for bleeding PUD, with a 15% to 20% rebleeding rate [78]. Neither is recommended as monotherapy [48,49,79]. Failure of ablative

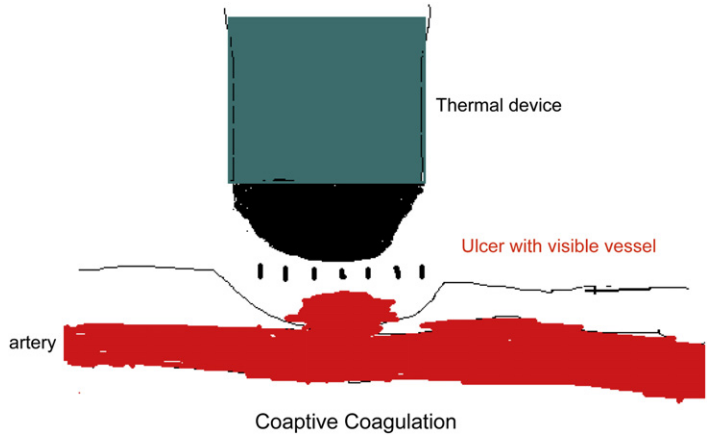


Fig. 4. Coaptive coagulation. Diagram shows a thermal probe (device) directly above a visible vessel within an ulcer. The thermal device would then be pressed firmly (coapted) on the visible vessel, under endoscopic guidance, while applying heat to close and seal the visible vessel to prevent rebleeding, just like a welder uses heat and applies force to fuse (weld) two pieces of metal together.

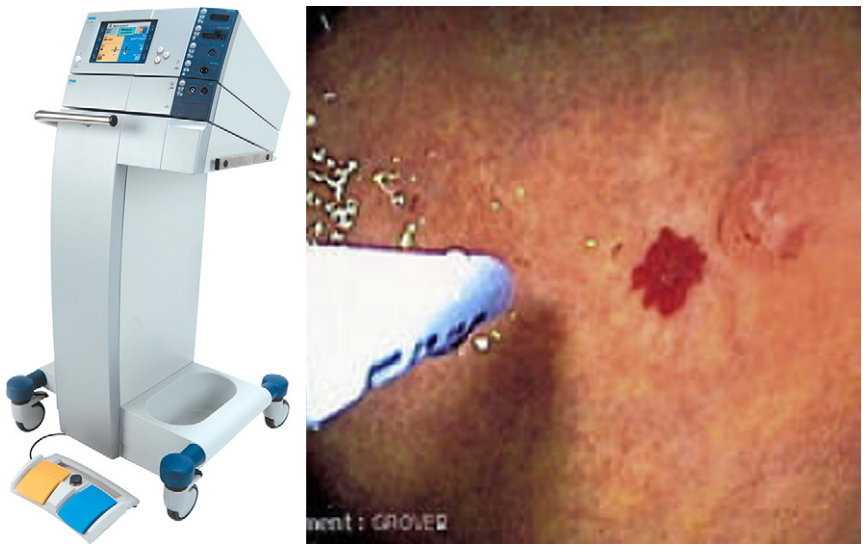


Fig. 5. Argon plasma coagulation (APC). Left photograph shows the apparatus, including the dials and monitor, together with the suction bottle mounted on a cart. The right endoscopic videophotograph shows an APC catheter in place within the channel of a therapeutic endoscope while applying ablative therapy to a large mucosal angiodysplasia. Note the catheter is not in direct contact with the lesion during APC application. (*Courtesy of* ERBE Elektromedizin GmbH, Tubingen, Germany; with permission.)

therapy is related to patient factors, such as significant comorbidities or coagulopathy, and ulcer factors, such as large, endoscopically inaccessible, or actively bleeding ulcers [11,57].

Mechanical therapy

In mechanical therapy, bleeding vessels are mechanically compressed to tourniquet the bleeding source. Mechanical therapy has a theoretic advantage in patients who have suboptimal hemostasis from cirrhosis, thrombocytopenia, or another coagulopathy. Metallic clips (endoclips) are the mechanical therapies of choice. They simulate surgical placement of hemostatic clips

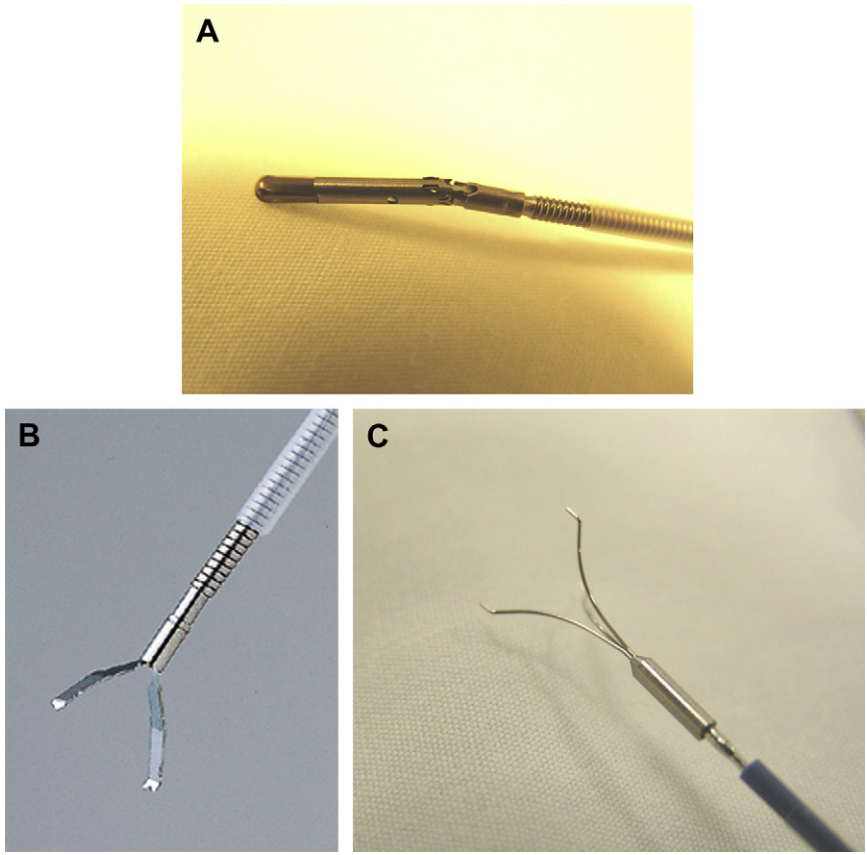


Fig. 6. Photographs illustrating the three different commercially available endoclips in the (*A*) closed state (*Courtesy of* Olympus America, Inc., Center Valley, PA; with permission) or (*B*) open state (*Courtesy of* Boston Scientific Co., Natick, MA; with permission). The manufactures are (*A*) Olympus Corporation, Center Valley, Pennsylvania; (*B*) Boston Scientific, Natick, Massachusetts; and (*C*) Wilson-Cook, Winston-Salem, North Carolina (*Courtesy of* Cook Endoscopy, Winston-Salem, NC; with permission). During endoscopy the completely opened endoclip is closed on a lesion and detached from the catheter.

(Fig. 6). Proper endoclip deployment requires a properly trained endoscopist and nurse-assistant. Deployment can be technically difficult in PUD because of a fibrotic ulcer base that is difficult to grasp, poor endoscopic visibility, awkward (acute) angle of deployment, and inadvertent clip dislodgment [74]. These technical problems can reduce efficacy [80,81]. Advanced patient age, proximal gastric lesions, and duodenal lesions are also associated with failed endoclip hemostasis [82].

Some studies report that endoclips are superior to ablative monotherapy, or even combined ablative and injection therapy, for ulcer hemostasis [83,84]. Endoclips provide useful markers to direct angiographic and surgical therapy [85]. Endoclips are being increasingly applied to various bleeding lesions, including iatrogenic bleeding after polypectomy, EMR, or sphincterotomy; and for bleeding from esophageal varices, or arterial lesions, such as the Dieulafoy lesion [86]. Some of these applications are insufficiently established. The efficacy of the three proprietary versions of endoclips is currently the subject of comparative clinical trials [87,88].

In endoscopic banding or ligation, a rubber band is deployed and contracts around a lesion that has been raised by endoscopic suction into a specially fitted, transparent endoscopic cap. It simulates surgical ligation for hemorrhage [89]. Banding is useful to treat larger (>2 mm) bleeding vessels. It is the endoscopic method of choice for bleeding esophageal varices [90]. The experience with banding for PUD, Mallory-Weiss tear, and Dieulafoy lesion is currently limited [91].

The detachable snare was developed for use before or after endoscopic polypectomy to prevent or to stop postpolypectomy bleeding, respectively. This device is being applied for hemostasis of other gastrointestinal lesions. These snares are tightly closed and left in situ around a lesion, without applying electrocautery, to tamponade internal vessels. Detachable snares are excellent for lesions that project into the lumen and are easily snared, such as pedunculated polyps, but are difficult to deploy on flat or excavated lesions, such as a typical ulcer. These devices have been successfully used to treat gastric varices, and have been used in scattered case reports for other causes of NVUGIB [92].

Combination hemostasis

Injection, ablative, and mechanical monotherapy have comparable efficacy for ulcer hemorrhage. Dual therapy is theoretically attractive to increase efficacy, but supporting evidence has only slowly accumulated. Although more effective than injection alone, dual therapy offers little advantage over ablative or mechanical monotherapy [7,49,84,93,94]. Combined epinephrine injection and thermocoagulation, using heater probe or bipolar electrocautery, reduces the rebleed rate to 5% to 15% from a 20% rate with injection monotherapy [49]. A meta-analysis has demonstrated the superiority of dual therapy over injection monotherapy in rebleeding, need for surgery, and mortality, but dual therapy had a moderate, but not statistically significant, trend toward

increased gastrointestinal perforation, probably related to thermocoagulation [95]. Combining epinephrine injection with endoclips is effective for ulcer hemostasis [93,96]. Endoclips are usually not deployed after ablative therapy for ulcer hemorrhage, but can be considered as salvage therapy before surgery [57,58].

The newest trend is to combine two modes of endoscopic therapy in one device. The newest Gold probe model incorporates a needle for injection therapy together with traditional electrocautery (Fig. 7). A novel device, the Cograsper (Olympus), combines electrocautery with mechanical therapy.

Non-ulcer upper gastrointestinal bleeding

Predominantly esophageal bleeding

Potential sources of esophageal bleeding include hemorrhagic reflux esophagitis, reflux-induced ulcers, caustic ingestion, primary esophageal malignancies, malignancies extending from the mediastinum, NSAID-induced or other pill esophagitis, nasogastric tube trauma, and esophagitis from infections, such as Candida, herpes simplex, cytomegalovirus, or HIV [97,98]. In a large series of acute UGIB, 2% bled from esophageal ulcers; 60% of these were associated with a hiatal hernia and 50% were related to NSAIDs [99]. Endoscopic therapy for point sources of acute esophageal bleeding includes epinephrine injection or ablative therapy. With pill esophagitis, the offending drug should be discontinued. Specific antimicrobial therapy is recommended for infectious esophagitis.

Reflux esophagitis

Endoscopic findings with reflux esophagitis include mucosal erythema, hypervascularity, edema, exudation, erosions, hemorrhage, and ulceration [100]. The injury is characteristically most severe just proximal to the gastroesophageal

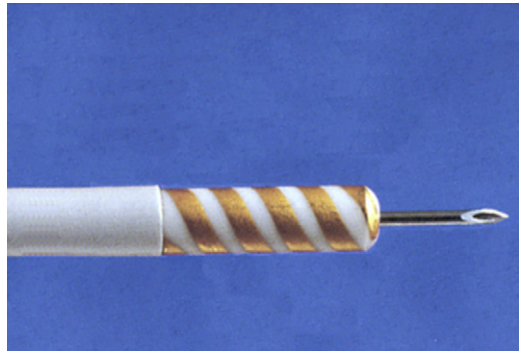


Fig. 7. Photograph shows a probe that provides for dual therapy. A central needle for injection therapy lies within a probe for electrical ablation therapy. (*Courtesy of* Boston Scientific Co. Natick, MA; with permission.)

junction. The severity of reflux esophagitis is classified, according to the Los Angeles grading system, as follows: A, one or more mucosal breaks less than 5 mm in length; B, at least one mucosal break greater than 5 mm but not continuous between the apices of adjacent mucosal folds; C, at least one mucosal break that is continuous between the tops of adjacent mucosal folds; and D, a mucosal break that involves at least three fourths of the luminal circumference [101].

Complications of reflux esophagitis include esophageal bleeding, Barrett esophagus, esophageal stricture, and esophageal ulcer. Barrett mucosa presents as islands or tongues of intensely erythematous mucosa extending from the gastroesophageal junction into the distal esophagus. It is associated with esophageal adenocarcinoma. An esophageal stricture from reflux esophagitis may be benign from acid-induced injury, or malignant from adenocarcinoma. Numerous biopsies should be obtained from a distal esophageal stricture to exclude severe dysplasia or adenocarcinoma.

Reflux esophagitis may cause bleeding from hemorrhagic esophagitis, benign esophageal ulcers, or an associated esophageal adenocarcinoma. Hemorrhagic esophagitis is difficult to treat with focal endoscopic therapy, such as epinephrine injection or thermocoagulation, because of the diffuse nature of the injury, but point sources of bleeding within hemorrhagic esophagitis may be considered for endoscopic therapy. Esophageal ulcers with high-risk SRH are amenable to injection or ablative therapy [102].

Mallory-Weiss tear

Tears at the gastroesophageal junction are a relatively common cause of NVUGIB. Patients typically present with hematemesis after repeated vomiting, retching, or coughing, often associated with an alcoholic binge, diabetic ketoacidosis, or emetogenic chemotherapy [103]. A Mallory-Weiss tear is rarely caused by EGD [23,104]. At EGD, a tear typically arises from the gastric side of the gastroesophageal junction; is linear and longitudinally arrayed; and manifests as a superficial ulcer, erosion, scab, or crevice depending on the stage of evolution and severity.

Bleeding from a Mallory-Weiss tear is typically mild to moderate, but can rarely be severe [105]. This mucosal laceration tends to heal rapidly because of its superficial nature and the abundant blood supply to esophageal mucosa. The bleeding spontaneously ceases in about 90% of cases [106]. Continued bleeding is often related to comorbidities, such as thrombocytopenia, other coagulopathies, or liver failure. The bleeding severity in cirrhotics correlates with the severity of liver dysfunction [105,107]. As for PUD, SRH include active hemorrhage, oozing, a visible vessel, or an adherent clot [108]. The indications for hemostasis are the same as for PUD [1,5,108,109]. Endoscopic hemostasis is unnecessary for relatively benign SRH, such as a pigmented flat spot [108]. The optimal endoscopic therapy for bleeding Mallory-Weiss tears (injection, ablative, or mechanical) is still being evaluated, and is likely to be influenced by technical factors and endoscopist preference [1,109]. Injection therapy, with epinephrine or a sclerosant, is effective [110,111], as is bipolar

electrocautery [111]. Mechanical therapy is being increasingly used. Endoscopic band ligation is as effective as injection [97,98]. Endoclips have proved effective either as monotherapy or after injection therapy [99,108]. It is unclear whether combination therapy improves hemostasis. Rarely, recurrent bleeding requires selective angiographic vasopressin infusion and gelatin sponge embolization, or surgery [111].

Esophageal varices

Esophageal varices constitute about 10% to 15% of UGIB, depending on the catchment area [112]. They typically produce severe UGIB that is associated with a high mortality [113]. Octreotide has replaced vasopressin as the pharmacotherapy for acute variceal bleeding because of less frequent and less severe side effects [114]. Other therapies include endoscopic banding or sclerotherapy, balloon tamponade, transjugular intrahepatic portal shunts (TIPS), and portosystemic surgical shunts [115]. This subject is reviewed in detail in the article by Drs. Toubia and Sanyal elsewhere in this issue.

Predominantly gastric lesions

Cameron lesion

Cameron lesions are gastric erosions or ulcers located within a hiatal hernia. They are detected at EGD in about 5% of patients who have a hiatal hernia [116]. Lesions are frequently multiple and are frequently associated with peptic esophagitis [116]. Most are asymptomatic. Clinical manifestations include chronic blood loss and iron deficiency anemia. They rarely cause acute UGIB [117,118]. The endoscopic therapy is similar to that for ordinary PUD [23,118]. Other therapies include PPIs and iron repletion for patients who have iron deficiency anemia. Surgical repair of the hiatal hernia is considered for chronic refractory bleeding.

Portal gastropathy

At EGD, portal gastropathy appears as moderate to intense erythema in a mosaic or snakeskin pattern surrounded by a pale, white, fine, reticular network in the proximal stomach. The erythema is attributed to saccular dilatation of mucosal capillaries and veins. Portal gastropathy is strongly associated with portal hypertension. In a study of 222 cirrhotic patients, about 25% had portal gastropathy [119]. Lesion risk factors include severe liver disease, gastric varices, and prior sclerotherapy or banding of esophageal varices because of gastric venous congestion [120]. This lesion sometimes causes overt or occult gastrointestinal bleeding from rupture of the friable, small, ectatic superficial vessels. In a series of 315 patients, only 8 (2.5%) patients had acute bleeding, and 34 (10.8%) patients experienced chronic bleeding from portal gastropathy [121].

Portal gastropathy is not amenable to endoscopic therapy because of its diffuse nature. It is treated by reducing the portal hypertension pharmacologically with propranolol, radiologically with TIPS, or surgically with portosystemic shunts [122]. In one study, only 35% of patients treated with propranolol bled compared with 62% of patients treated with placebo [123]. In a study of 40 patients who mostly had mild portal gastropathy, the blood transfusion requirements decreased by 89% after TIPS [124]. Patients who bled from portal gastropathy associated with advanced liver failure should undergo liver transplantation [125].

Benign and malignant gastric tumors

Mesenchymal tumors, including gastrointestinal stromal tumors (GISTs) and leiomyomas, constitute about 1% of primary gastrointestinal tumors [126]. They most commonly occur in the stomach. GIST tumors nearly always express c-kit receptor, a membrane tyrosine kinase receptor, and are derived from the interstitial cells of Cajal, which function as the gastrointestinal pacemaker cells. Leiomyomas do not express this receptor and are derived from smooth muscle cells. Both tumors often present with overt UGIB. For example, in a series of 80 patients who had these tumors about 45% presented with acute UGIB [127]. At EGD, nonbleeding leiomyomas appear as a submucosal mass, covered by normal mucosa that has smooth margins and bulges into the lumen. Bleeding lesions, however, often have central mucosal ulceration from local mucosal ischemia. Lesions typically range from about 1 to 5 cm in diameter. Although usually benign, they are potentially malignant. Routine endoscopic biopsies are often nondiagnostic because of the deep lesion location within the bowel wall. The pathologic diagnosis requires deep endoscopic biopsies using the biopsy on biopsy (well) technique or endosonographic guidance. The endosonographic finding of a smooth mass localized to the muscularis propria is characteristic of leiomyoma. Microscopically, spindle or epithelioid cells occur in fascicles or whirls, without nuclear atypia and with rare mitoses. Possible malignancy is suggested by endosonographic findings of lesion size greater than 30 to 50 mm, tumor disruption of normal tissue planes, focal cystic lesions, and adjacent lymphadenopathy; and by histopathologic findings of abundant intracellular cytoplasm, presence of multinucleated giant cells, and an increased concentration of mitoses (>5 per high power field) [128]. Lesions usually require complete segmental resection [129].

Gastric lymphomas constitute about 5% of gastric tumors [130]. Gastric MALTomas (for mucosa-associated lymphoid tissue) are early B cell lymphomas. They commonly cause chronic occult gastrointestinal bleeding but rarely cause acute bleeding. Endoscopic findings include a polypoid mass; a gastric ulcer; or thickened cerebroid gastric folds. They may also present as relatively innocuous-appearing gastric nodularity. Gastric lymphomas, including MALTomas, can extend from the stomach across the pylorus into the duodenum, a growth pattern not exhibited by gastric adenocarcinomas.

Standard endoscopic biopsies are often nondiagnostic because of the deep submucosal location of MALTomas. The diagnostic yield of endoscopic biopsies is increased by use of jumbo biopsies or of biopsies on biopsies, using the well technique. Pathologically, MALToma is characterized by an infiltrate of lymphocytes and plasma cells that express the standard B cell antigens. Immunophenotyping can diagnose lymphoma and differentiate MALTomas from other lymphomas.

MALTomas are highly associated with chronic *H pylori* infection. Chronic *H pylori* infection stimulates proliferation of B lymphocytes that can result in genetic mutations, particularly chromosome 11:18 translocation, that leads to unregulated proliferation of transformed B cells. Early diagnosis is important because early lymphoma often responds to *H pylori* eradication. From 50% to 80% of MALTomas exhibit complete histologic regression after *H pylori* eradication [131,132].

Other primary or metastatic gastric malignancies can produce UGIB. Adenocarcinoma is the most common primary malignancy. It presents as a gastric mass, ulcerated mass, nonhealing ulcer, or stricture. Endoscopic differentiation of a malignant ulcer from a benign ulcer was considered under the section on PUD. In linitis plastica the stomach appears poorly motile and noncompliant because of diffuse infiltration of adenocarcinoma throughout the gastric wall. Gastric metastases most commonly arise from lung cancer, breast cancer, and cutaneous melanoma [133]. An eroded polypoid or submucosal mass is a common endoscopic appearance [133,134]. Endoscopic hemostasis of gastric malignancies is usually achieved by ablative therapy, epinephrine injection, or both [134]. These malignancies commonly rebleed, however, and generally have a poor long-term prognosis. UGIB after chemotherapy or radiotherapy for gastric malignancy is difficult to manage and often requires a multidisciplinary approach [135].

Dieulafoy lesion

A Dieulafoy lesion is a congenital, abnormally large, submucosal artery that has a potential to bleed through a small mucosal defect [136]. It accounts for about 2% of all NVUGIB [109,137]. Patients typically present with acute, severe UGIB, often associated with manifestations of hemodynamic compromise, such as hypotension or orthostasis. EGD reveals a pigmented protuberance, representing the vessel stump, with minimal surrounding erosion and no ulceration. In contrast, a pigmented protuberance within an ulcer is a visible vessel within a peptic ulcer. In 75% of cases the Dieulafoy lesion is located in the proximal stomach about 6 to 10 cm below the gastroesophageal junction along the lesser curvature, but it can occur throughout the gastrointestinal tract [136]. The lesion is typically only 2 to 5 mm in diameter. The lesion can be missed at EGD because it is so small and inconspicuous or because it is obscured by blood or clots. It may be associated with advanced liver disease [138]. Endoscopic biopsy of the lesion is contraindicated because of the risk of inducing bleeding.

Endoscopic therapy is particularly attractive for this point source of bleeding because of the propensity of this lesion to bleed frequently and massively, and its high mortality without endoscopic therapy. Hemostasis is accomplished with epinephrine injection; ablative therapy, including APC; or mechanical therapy, including band ligation or endoclips. In two large reviews, long-term hemostasis was achieved in about 90% of patients by various endoscopic therapies [139,140]. For example, endoscopic injection, with epinephrine or polidocanol, achieved hemostasis in 53 of 56 patients [54,55,141]. There is a recent trend toward mechanical therapy [109,138,142,143]. The lesion is particularly amenable to mechanical therapy because of its focal nature and protuberant shape. Band ligation and endoclips have comparable efficacy [143]. There is a concern about ulceration after mechanical therapy, especially after band ligation [109,144]. Up to 20% of patients require surgery because of recurrent hemorrhage [145]. A wide, wedge resection of the lesion and surrounding tissue is recommended [146]. The mortality of this lesion has declined from about 25% in the 1980s to about 10% now because of aggressive application of endoscopic therapy [147].

Angiodysplasia

Angiodysplasia accounts for about 2% to 5% of acute UGIB [148]. Upper gastrointestinal angiodysplasia occurs most commonly in the stomach, sometimes in the duodenum, and rarely in the esophagus [149]. Angiodysplasias are often multiple, and tend to be clustered when multiple [150]. Histologically, angiodysplasias consist of dilated, tortuous, and thin-walled vessels lined by endothelium with no or little smooth muscle and no inflammation, fibrosis, or atherosclerosis [151]. Angiodysplasia tends to occur in the elderly. Bleeding from angiodysplasia is believed to be associated with chronic renal failure [152], aortic stenosis [153], and CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome [154]. The nature and strength of the first two associations is somewhat controversial. The association with aortic stenosis likely arises from bleeding from previously clinically silent angiodysplasia caused by loss of large multimers of von Willebrand factor from high shear forces across a stenotic aortic valve [155].

At EGD, angiodysplasia appears as a dense, macular and reticular network of vessels (vascular tuft), which is typically 2 to 8 mm wide and is intensely red because of the high oxygen content of erythrocytes within vessels supplied by arteries without intervening capillaries [156]. Angiodysplasia may become inconspicuous at EGD in a patient who has hypotension or profound anemia, and may be obscured by meperidine administration [157]. Endoscopic biopsy is not recommended for the diagnosis because of the risk of inducing bleeding and the characteristic endoscopic appearance.

Angiodysplasias often are asymptomatic, incidental findings. For example, in a review of 41 patients who had upper gastrointestinal

angiodysplasia, 21 (51%) were incidental endoscopic findings [158]. It is therefore important to assess at EGD whether an observed angiodysplasia is the source of UGIB. Up to 30% to 45% of patients who have angiodysplasia have other gastrointestinal lesions, which are more likely the cause of the bleeding [159]. Bleeding is attributed to angiodysplasia only when it is active bleeding, has an overlying clot, or all other causes are excluded. In a retrospective comparison of angiodysplasia with other causes of gastrointestinal bleeding, patients who had angiodysplasia had a milder hospital course with fewer transfusions of packed erythrocytes, shorter hospitalizations, and lower mortality [149].

An asymptomatic angiodysplasia, incidentally discovered at EGD, is generally not treated endoscopically because of a low likelihood of subsequent bleeding [148,160]. Endoscopic therapy may, however, be considered when an incidental angiodysplasia is exceptionally large or when prior bleeding from an angiodysplasia is suspected but undocumented. In other clinical situations, a graded approach to therapy is predicated on the likelihood of further bleeding from angiodysplasia [156]. Angiodysplasias that recently bled, as demonstrated by SRH, are treated at EGD. An angiodysplasia associated with otherwise unexplained iron deficiency anemia may be treated at EGD depending on the clinical scenario.

At EGD, actively bleeding angiodysplasias are sometimes first injected by epinephrine or alcohol, followed by thermocoagulation, electrocoagulation, or photocoagulation [161]. These endoscopic therapies are relatively safe and efficacious. For example, Gostout and colleagues [162] reported cessation of bleeding in 72 of 83 patients (87%) after laser photocoagulation during a mean follow-up of 12 months. Laser therapy, however, has a perforation rate of up to 4% attributable to deep mural injury [163]. Endoscopists therefore prefer thermocoagulation or electrocoagulation over photocoagulation.

APC is emerging as the endoscopic therapy of choice because of relatively low risks owing to the shallow depth of tissue injury and high efficacy because of the superficial, mucosal location of angiodysplasia. Among 100 patients undergoing APC for colonic angiodysplasia for either overt gastrointestinal bleeding or iron deficiency anemia and fecal occult blood, 90 patients (90%) did not require any blood transfusions during a mean follow-up of 20 months [164].

An actively bleeding angiodysplasia that is refractory to endoscopic therapy may be treated by angiographic embolization. This procedure has a high success rate [165,166]. Improved catheter design and superselective catheterization with more distal embolization have recently reduced the frequency of intestinal infarction from angiographic embolization. Surgery is reserved for severe bleeding from well-characterized and localized lesions refractory to endoscopic or angiographic therapy. EGD, colonoscopy, and capsule endoscopy should be performed preoperatively to exclude distant synchronous gastrointestinal angiodysplasia or other lesions [150].

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia is a rare genetic vascular disorder caused by mutation of the *ENG* (endoligin) gene (type I) or the *ACVRL1* gene (type II) and characterized by multiple orocutaneous and mucosal telangiectasias, especially in the nose and gastrointestinal tract [167]. About 25% of affected patients experience clinically significant gastrointestinal bleeding, which typically begins during middle age [168]. Chronic gastrointestinal blood loss may cause iron deficiency anemia, whereas acute blood loss may cause hypovolemia and hypotension. The diagnosis is straightforward in patients who have the clinical triad of telangiectasia, recurrent epistaxis, and a compatible family history [169]. The site and source of UGIB is diagnosed by EGD. The endoscopic appearance of telangiectasia resembles that of nonsyndromic angiodysplasia or of cutaneous telangiectasia occurring in this syndrome. Lesions tend to be widespread throughout the gastrointestinal tract.

The endoscopic therapy resembles that for nonsyndromic angiodysplasia, but endoscopic therapy is complicated by lesion multiplicity, widespread dissemination, and progression over time. Isolated actively bleeding telangiectasias are usually successfully treated, but patients often rebleed from other, untreated gastrointestinal telangiectasias, and therefore require multiple endoscopic sessions [170]. A few small studies have suggested that estrogen-progesterone therapy may decrease the rate of chronic gastrointestinal bleeding from these telangiectasias [171], but this therapy is controversial [172]. Patients generally require iron supplementation because of recurrent gastrointestinal blood loss.

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE) usually occurs in females and in the elderly [173]. It commonly presents with iron deficiency anemia, sometimes presents as an incidental finding, and occasionally causes acute UGIB. The patient may have a long history of chronic gastrointestinal bleeding, with multiple prior blood transfusions, because of delayed diagnosis. GAVE is associated with chronic renal disease and, possibly, chronic liver disease, but is not associated with portal hypertension without liver disease [112]. EGD reveals parallel folds that radiate from the pylorus to the proximal antrum. The folds contain intensely erythematous linear streaks at their apices. GAVE is also called the watermelon stomach because these linear streaks resemble the stripes on a watermelon rind [174]. GAVE is differentiated from ordinary antral gastritis by its location on folds, blanching on pressure, and sharp lesion demarcation [173]. GAVE can be safely biopsied with only minimally increased and minor bleeding because of its low intravascular pressure. Biopsy may reveal characteristic findings of dilated, tortuous mucosal capillaries often occluded by bland fibrin thrombi and dilated submucosal veins without inflammatory infiltration [175].

Pharmacotherapy, including histamine-2 receptor antagonists and PPIs, are ineffective because this lesion is not acid related and patients often have hypochlorhydria from atrophic gastritis [176]. Endoscopic therapy is the primary therapy. From 87% to 100% of patients have stable hematocrits without blood transfusions for several years after endoscopic therapy [177]. Endoscopic thermal therapy used to be frequently performed, but it requires many sessions because of the large extent of the lesion. Although laser therapy is frequently successful and requires few endoscopic sessions, it is being used less frequently because of a modest risk for severe complications, high cost, and poor machine availability. APC therapy may become the therapy of choice because of the diffuse nature and superficial location of the lesion [178,179]. APC is well tolerated and safe because it produces only shallow tissue injury [180]. APC diminishes blood transfusion requirements, although several sessions are usually required [180,181]. Combining the results of four studies, 50 of 55 transfusion-dependent patients required no transfusions after APC therapy, during a mean follow-up of approximately 2 years [181–184]. It is important to differentiate GAVE from portal gastropathy because the former responds to endoscopic therapy but does not respond to portal pressure reduction [185], whereas the latter does not respond to endoscopic therapy but responds to portal pressure reduction [109]. Antrectomy is recommended if endoscopic hemostasis fails. It removes the lesion and nearly always cures the disease, but entails significant morbidity and 5% mortality [186].

Gastritis

Acute hemorrhagic gastritis can result from aspirin or NSAID use, radiation, toxic ingestion, and infection, such as cytomegalovirus or syphilis [187]. Stress-related mucosal disease (SRMD) refers to erosive gastritis in patients experiencing severe physiologic stress from critical diseases, especially overwhelming sepsis or respiratory failure requiring mechanical ventilation [188]. Patients often are in the ICU with multiple medical problems. The pathophysiology involves gastric mucosal ischemia and acid-mediated injury [188,189]. Patients who have SRMD usually experience mild bleeding [188,190]. EGD typically reveals multiple superficial ulcers with surrounding erythema. Treatment of the underlying disease that caused the SRMD is essential for lesion healing. PPIs have an established role in treating SRMD, but their role in preventing SRMD is not well validated [190,191]. Acid-suppressive agents do not diminish mortality or the already low rate of clinically significant UGIB in ICU patients, but might increase the risk for pneumonia [191]. Other medications, such as histamine-2 receptor antagonists, have a lower risk for causing pneumonia and are cheaper, but their use in SRMD has also not been validated [192]. The current consensus is not to routinely administer PPIs or other agents as prophylaxis against UGIB in ICU patients [188,190].

Nasogastric tube erosions

Nasogastric tube erosions occasionally cause gross UGIB, but this bleeding is characteristically mild and rarely requires blood transfusions. For example, in a review of 152 nasogastric tube insertions for gastrointestinal bleeding after myocardial infarction, only one patient had nasogastric tube–induced gastric erosions at EGD that required blood transfusions [29]. Nasogastric tube erosions appear at EGD as multiple, colinear, round, and relatively uniform erythematous erosions that are in register with the apertures of the nasogastric tube and that are at the same stage of evolution because of their simultaneous creation [193]. They typically occur in the stomach along the greater curve where the nasogastric tube tends to lodge. These erosions do not require endoscopic therapy. They are generally treated by nasogastric tube removal, if possible, and PPI therapy.

Duodenal lesions

Anastomotic ulcers

Marginal ulcers can develop distal to the gastrojejunal anastomosis after PUD surgery (Billroth II) and can cause UGIB. UGIB is being increasingly reported from marginal ulcers after gastric bypass surgery or vertical banded gastroplasty because of the increasing popularity of these bariatric surgeries [194]. Marginal ulcers occur in 4% to 7% of patients who have gastric bypass, and cause bleeding in 1% to 3% of patients after these surgeries [195,196]. The pathophysiology may be multifactorial, including bile reflux gastritis, inadequate prior surgery, local ischemia from vessel ligation, gastric stasis, and exposure to gastrotoxic medications, such as NSAIDs [197]. At EGD, the afferent and efferent loops of a Billroth II should be intubated and examined, and the anastomosis carefully inspected. Endoscopic intubation of a bypassed intestinal limb after bariatric surgery may be technically challenging and require an enteroscope or colonoscope for access [198]. Endoscopic manifestations of anastomotic injury include erosions, friability, ulcers, fibrosis, small polyps, and disrupted sutures [199]. The endoscopic therapy for bleeding from marginal ulcers is the same as for ordinary ulcers. Postprocedure management typically includes PPI therapy and investigation for *H pylori* infection [196].

Aortoenteric fistula

Aortoenteric fistula often presents with a mild "herald bleed" followed by massive bleeding [200]. It constitutes an indication for emergency EGD because of a high mortality with delayed diagnosis. It is rare. It is strongly associated with prior aortic surgery, aortic aneurysms, and severe atherosclerosis [201]. EGD should be performed up to the distal duodenum when this fistula is suspected because this fistula usually occurs at this location. At EGD a mesh from a prosthetic graft may be identified. If

this lesion is identified at EGD, the EGD should be aborted without attempting endoscopic therapy because of the risk of massive bleeding when tampering with this lesion. The lesion is treated surgically. The mortality is high [202].

Postprocedural bleeding

Postprocedural bleeding is usually related to endoscopic biopsy or therapy [23]. Hemobilia, defined as blood coming from the bile ducts, usually occurs after a procedure, such as endoscopic sphincterotomy, liver biopsy, percutaneous transhepatic cholangiography, TIPS, or cholecystectomy, but may arise from hepatobiliary disease, such as malignancy, polyps, or cysts. Postsphincterotomy bleeding usually responds to balloon tamponade or epinephrine injection, but may require thermocoagulation or endoclip placement [203]. Blood in the gastrointestinal tract arising from the pancreas, or hemosuccus pancreaticus, usually results from chronic pancreatitis, pancreatic pseudocysts, pancreatic tumors, or blunt trauma to the pancreas, and from therapeutic endoscopy, including pancreatic stone removal, pseudocyst drainage, or pancreatic duct stenting.

Small intestinal bleeding

Small intestinal bleeding beyond the ligament of Treitz is most commonly caused by angiodysplasia, but may be caused by Crohn disease, Meckel diverticulum, jejunoileal ulcers, including ulcers related to NSAIDs or gastrinomas, ectopic varices, hemangiomas, masses, polyps, and submucosal lesions [204]. Hematemesis is unusual. The stool may appear bloody, melanotic, gray, or normal depending on the location and tempo of the bleeding [1,205].

Obscure gastrointestinal bleeding is defined as continuous or intermittent gastrointestinal bleeding that is not diagnosed by EGD and colonoscopy. It represents a diagnostic and therapeutic challenge [206]. Such bleeding is now evaluated by capsule endoscopy and single- or double-balloon enteroscopy [207,208]. Although it usually arises from small intestinal bleeding beyond the ligament of Treitz, occasionally repeat EGD or colonoscopy may reveal a previously missed lesion, such as a Dieulafoy lesion. The expanding therapeutic armamentarium available with double-balloon enteroscopy includes injection, ablative therapy (including APC), and variceal sclerotherapy [209]. Older technologies, including push enteroscopy, angiography, enteroclysis, and intraoperative endoscopy, are used to investigate obscure gastrointestinal bleeding when these new technologies are unavailable [206,210].

Postendoscopy care

EGD assists in patient triage. Those who have low-risk SRH may be downgraded to a lower level of hospital care or, rarely, even promptly discharged [2,11,109,211]. PPI therapy should be continued after EGD for

NVUGIB, but the optimal dose and route remains unclear [54,55,212]. Intravenous PPI therapy is expensive, but this cost is offset by its reducing the need for blood transfusions and the hospital length of stay [213]. All patients who have bleeding PUD and *H pylori* infection should receive triple therapy because infection eradication diminishes the rebleeding rate compared with PPI therapy alone [214]. The duration of PPI therapy after therapeutic EGD for PUD is unclear. The duration is much shorter if *H pylori* is eradicated and NSAIDs are avoided [214]. PPIs help prevent rebleeding from peptic ulcers in patients administered aspirin or NSAIDs, but these drugs should be avoided, if possible, in patients who have known PUD [215]. Mild to moderate anticoagulation only modestly increases the risk for severe rebleeding after endoscopic therapy for NVUGIB [216].

Repeat esophagogastroduodenoscopy

Repeat (second look) EGD after therapeutic endoscopy is controversial and not routinely recommended [109]. Repeat EGD has the greatest benefit for patients who have high-risk SRH, but this practice raises concerns about gastrointestinal perforation if ablative therapy is repeated [217]. A meta-analysis showed that systematic repeat EGD reduces the rebleeding rate but does not diminish the need for surgery or the mortality [218]. Most rebleeding occurs within 72 hours of the initial EGD [57]. Occasionally, the bleeding lesion is missed at the initial EGD and identified only at a repeat EGD [219,220].

Refractory hemorrhage

Overall, 5% to 15% of patients who have NVUGIB rebleed despite endoscopic therapy. Reversal of any severe coagulopathy, by platelet or fresh frozen plasma transfusions, is essential for endoscopic hemostasis. Patients who have refractory bleeding are candidates for angiography or surgery. The decision regarding a particular therapy requires a team approach with input by the gastroenterologist, surgeon, interventional radiologist, and intensivist. Even when endoscopic hemostasis fails, EGD is important before angiography or surgery to diagnose the site and cause of the bleeding. This information helps the angiographer plan which of the major mesenteric vessels, among the celiac axis, superior mesenteric artery, or inferior mesenteric artery, to first catheterize; which branches to selectively catheterize; and what hemostatic agents to use. This information helps the surgeon plan the surgical incision and approach, whether thoracic, upper abdominal, or lower abdominal; which organ to target for surgery; and what type of surgery to perform (eg, antiulcer surgery versus wedge resection for a Dieulafoy lesion).

The armamentarium of the interventional radiologist includes vasoconstrictor agents, such as vasopressin, or embolic agents, such as a gelatin sponge or microcoils, for selective occlusion of a bleeding artery. Rebleeding is common after radiologic intervention. Complications of radiologic intervention include gastrointestinal ischemia and infarction [221].

The specific operation for NVUGIB reflects the local expertise. Surgery for PUD optimally combines control of hemorrhage with acid-reduction procedures [222]. Peptic ulcer surgery is less commonly performed than previously because of endoscopic hemostasis, PPI therapy, and *H pylori* eradication, but it still constitutes a significant proportion of gastrointestinal surgery in urban and Veterans Administration hospitals. The mortality of this surgery is greater than 20% [223]. Patients often experience significant morbidity after gastrointestinal surgery [223].

Future challenges and prospects

Aggressive endoscopic therapy for NVUGIB has resulted in a decreased need for surgery and blood transfusions, shorter hospital stays, and lower costs, but approximately 5% to 15% of patients rebleed [58,224]. Further research should clarify the clinical roles of the current endoscopic therapies and refine the therapeutic algorithm to further reduce the risk of rebleeding. Epinephrine remains the gold standard for injection therapy, until the technical and safety issues for endoscopic glues are clarified [69–71]. BICAP electrocautery and heater probe continue to be the principal ablative therapies, although APC is useful for diffuse lesions, such as GAVE, and is being increasingly applied for point sources of bleeding, such as the Dieulafoy lesion. Cryotherapy is still experimental for UGIB [225]. The clinical roles of the existing mechanical therapies need to be better defined and validated [48,58].

Regarding endoscopic therapy for SRH with PUD, the endoscopic approach to an adherent clot on an ulcer needs clarification [51–53]. The endoscopic therapy for many other upper gastrointestinal lesions, such as Mallory-Weiss tears and Dieulafoy lesions, needs to be standardized.

Exciting new mechanical therapies are being developed. NOTES (natural orifice transendoscopic surgery) is stimulating development of endoscopic suturing devices to close gastrointestinal perforations [226]. As such suturing devices become more sophisticated and versatile, they will be increasingly adapted to control gastrointestinal bleeding (eg, to endoscopically oversew bleeding ulcers). Experimental suturing devices may become a standard mechanical therapy for NVUGIB [226,227]. Novel devices that combine two therapies in one device, such as a probe that combines injection therapy with electrical ablation, or a device that combines electrocautery with mechanical therapy, need further study before achieving widespread clinical application. Undoubtedly, other devices offering multimodal therapy will be developed in the near future.

Doppler ultrasound evaluation of ulcer vessels may determine the need for and predict the effectiveness of endoscopic therapy [228]. Management of NVUGIB may be affected by the recent ''pay for performance'' trend which provides incentives for optimal triage and early discharge [229].

For low-risk patients, clinical assessment and endoscopic results should be better communicated and used for earlier discharge [15,17]. Clinical

scoring systems will be further refined to improve patient prognostication and facilitate earlier patient discharge. PPIs have been validated for high-risk hemorrhage from PUD, but guidelines still need to be clarified concerning the PPI dosage, formulation, and duration of therapy [54,55].

Summary

Acute UGIB is a relatively common, potentially life-threatening emergency that requires rapid patient assessment, proper triage, and rapid institution of resuscitative measures. EGD is the principal diagnostic, therapeutic, and prognostic modality for NVUGIB. Endoscopic therapy reduces the rate of rebleeding, blood transfusion requirements, and need for surgery. Administration of PPIs is important for NVUGIB.

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