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Evaluation and management of Non-variceal upper gastrointestinal bleeding

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ABSTRACT

Non-variceal upper gastrointestinal bleeding continues to be an important cause of morbidity and mortality. The most common causes include peptic ulcer disease, Mallory–Weiss syndrome, erosive gastritis, duodenitis, esophagitis, malignancy, angiodysplasias and Dieulafoy's lesion. Initial assessment and early aggressive resuscitation significantly improves outcomes. Upper gastrointestinal endoscopy continues to be the gold standard for diagnosis and treatment. We present a comprehensive review of literature for the evaluation and management of non-variceal upper gastrointestinal bleeding.

Introduction

Upper gastrointestinal bleeding is defined as bleeding proximal to the ligament of Treitz without evidence of esophageal, gastric, and duodenal varices.[1] Gastrointestinal bleeding (GIB) is a

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significant public health issue costing nearly five billion dollars annually to the health system.[2] Although, the incidence rates vary widely based on geographic location, prior studies have consistently shown higher incidence among males and the elderly population.[3] In 2012, approximately 1,80,767 patients were hospitalized with UGIB.[2] Recent studies have shown a decrease in mortality which is likely due to the advent of proton pump inhibitors (PPI), improved detection and treatment of *Helicobacter pylori* (*H. pylori*), and advances in endoscopic and interventional radiologic techniques.[3,4] The most common cause continues to be peptic ulcers, although the incidence has declined.[5] Despite endoscopy being the definitive diagnostic and therapeutic modality, a fundamental knowledge of the different etiologies and appropriate management is needed for emergency medicine physicians, intensivists, surgeons, interventional radiologists, internists, and gastroenterologists.

Etiology

Peptic ulcers are mucosal erosions that extend through the muscularis mucosa into deeper layers of the wall. Peptic ulcers are the most common form of non-variceal upper gastrointestinal bleeding (NVUGIB) accounting for about 31–67% of upper gastrointestinal bleeding.[5–8] The recent decline in incidence of peptic ulcers is thought to be due to increase in PPI use, affective *H. pylori* treatment, and awareness of nonsteroidal anti-inflammatory drugs (NSAIDS) as a cause of peptic ulcers. Peptic ulcers can be present in either the stomach or bulb of duodenum and are most commonly caused by *H. pylori* and NSAID use. *H. pylori* attaches to the gastric and duodenal mucosa inducing tissue injury by several mechanisms.[9] NSAIDS continue to be a common cause for peptic ulcers.[10,11] Injury is caused by the local and systemic effects of prostaglandin inhibition.[12]

Other causes of upper GIB include esophagitis, gastritis, and duodenitis which are inflammatory processes that can further progress to ulcerations and have similar risk factors as peptic ulcers[13] (Table). Mallory–Weiss syndrome is caused by longitudinal mucosal tears at the gastroesophageal junction or gastric cardia due to a rapid increase in intraabdominal pressure which is usually caused by vomiting or retching.

Vascular lesions including angiodysplasia, Dieulafoy's lesions, and gastric antral vascular ectasia (GAVE) cause 2–8% of NVUGIB.[5,6,8] Angiodysplasias, vascular ectasia, or arteriovenous malformations (AVM) can be used synonymously and refer to thin-walled tortuous vessels found throughout the gastrointestinal tract. The pathogenesis of AVMs is not completely understood, but they are frequently found in individuals with aortic stenosis (Heyde's syndrome), Von Willebrand disease, and chronic renal failure.[14] Dieulafoy's lesions are dilated submucosal arteries (1–5 mm) that infiltrate into the mucosa in the absence of an overlying ulceration.[15] The exact mechanism of Dieulafoy's lesions is not completely understood at this time, but several mechanisms have been proposed. It is seen more commonly in men and patients with comorbidities that include DM, HTN, cardiovascular diseases, and chronic kidney disease.[15–18] Neoplasms of the upper gastrointestinal tract can arise from any type of cell line whether local or metastatic, and can also lead to upper GIB due to superficial erosions or via invasion into the vasculature.

Table
Etiologies of non-variceal upper gastrointestinal bleeding.

Etiology	Frequency
Peptic ulcer	26–59%
Mallory–Weiss tear	7–12%
Erosive gastritis/duodenitis	7–28%
Esophagitis	4–12%
Malignancy	4–6%
Angiodysplasia	2–8%
Other	2–11%

Evaluation

Initial assessment of the patient with acute GIB includes a focused history, physical exam, hemodynamic assessment, and laboratory studies. All of these are instrumental in guiding further management. The most common presentations of upper GIB include hematemesis, coffee-ground emesis, hematochezia, and melena. Hematemesis can present with bright red blood or clots which denotes active bleeding. Coffee-ground emesis is a less active bleed and has a speckled brown color. Melena is present with dark tarry stools and experts suggest that it has a significant odor. A brisk massive upper GIB can also present as hematochezia due to the blood causing catharsis and passing through the gastrointestinal tract quickly. The history of the patient, if they are not unconscious, usually helps in establishing the diagnosis. The common etiologies of NVUGIB can be determined

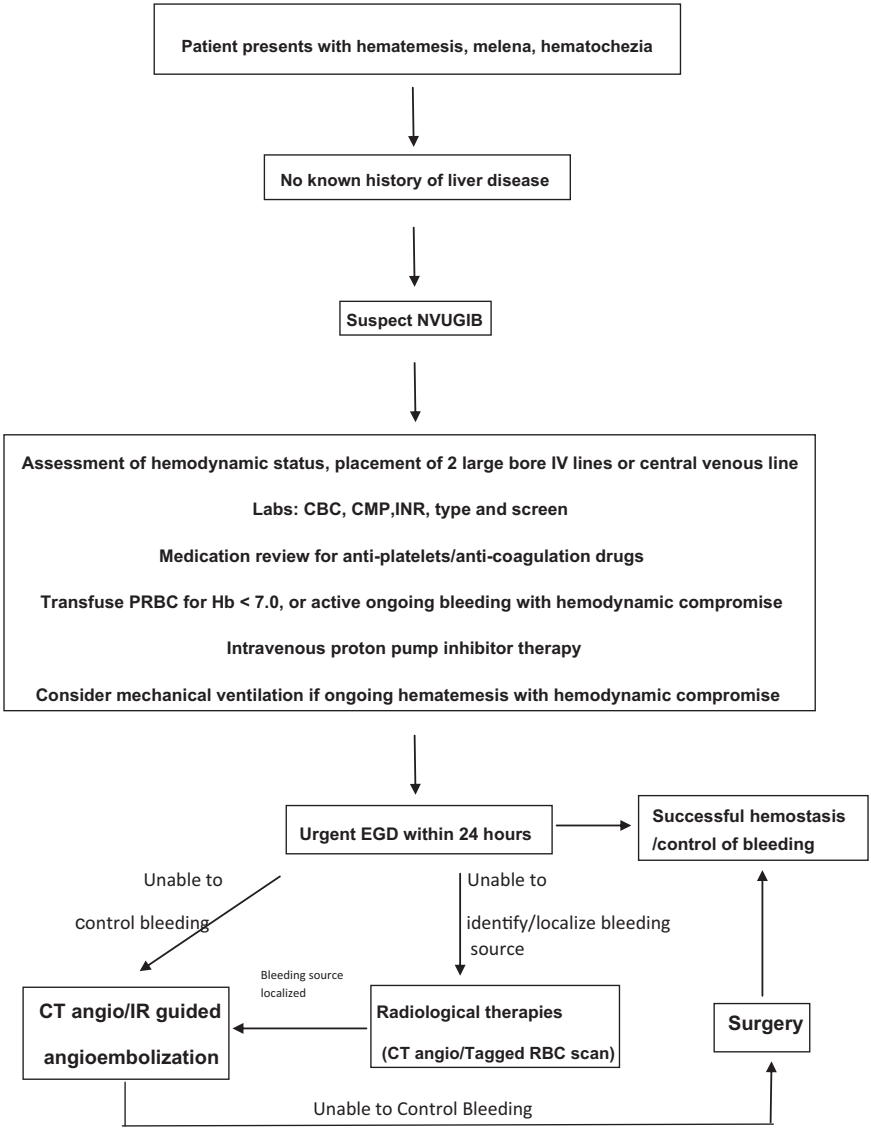

Fig. Initial evaluation and management of non-variceal upper gastrointestinal bleeding.

while discussing presenting symptoms, underlying medical issues, medications, surgeries, and previous episodes of bleeding. During the physical exam, assessment should focus on the signs of hypovolemia and anemia with a thorough abdominal exam. The rectal exam and the observation of stool is an indispensable portion of the physical exam in patients with suspected GIB and should be performed. Each patient should have a complete blood count, basic metabolic panel, hepatic function panel, and coagulation studies ordered. Type and screening for blood transfusion should be done in all patients with significant GIB.

Many scoring systems have been devised to address and provide prognostic information for patients that present with NVUGIB. These scoring systems guide physicians regarding appropriate clinical intervention, level of care, rebleeding risks, discharge planning, and mortality. Despite these, prior reports have shown that only a small percentage of physicians across all specialties use a risk assessment score while making clinical decisions.[19] The American College of Gastroenterology and the European Society of Gastrointestinal Endoscopy have now both recommended the use of risk assessment tools to determine high versus low-risk patients to plan appropriate management.[20,21] The most commonly used assessment tools are the Rockall score, Glasgow Blatchford score, AIMS65, Baylor bleeding score, and the Cedar-Sinai Medical Center predicative index. The assessment tools can be divided into pre-endoscopic (Glasgow Blatchford score and AIMS65) and post-endoscopic (Rockall score, Baylor bleeding score, and Cedar-Sinai Medical Center predicative index). The Rockall score uses age, shock (systolic blood pressure and pulse), comorbidities, diagnosis, and recent signs of hemorrhage.[22] If the initial three questions are only tabulated, this is considered the clinical Rockall score and can be used prior to endoscopy. The Glasgow Blatchford scale criteria include: blood urea nitrogen, hemoglobin (for men or women), systolic blood pressure, tachycardia, melena, syncope, hepatic disease, and cardiac failure.[23] The AIMS65 criteria include: albumin less than 3.0 g/dL (30 g/L), INR $>$ 1.5, altered mental status (Glasgow coma score $<$ 14, disorientation, lethargy, stupor, or coma), systolic blood pressure of 90 mmHg or less, age older than 65 years.[24] The Baylor bleeding score includes: age, comorbidities, severity of illness, site of bleeding, and stigmata of bleeding.[25] The Cedar-Sinai Medical Center predicative index includes: endoscopic findings, timing of symptom initiation to hospitalization, hemodynamics, and comorbidities.[26]

Management

Prior to endoscopy (Fig.)

When evaluating patients with NVUGIB, ensuring adequate oxygen saturation is a priority and intubation is an option to maintain the airway in patients with altered mental status or concern for aspiration due to hematemesis. We suggest that the need for mechanical ventilation should be assessed on a case-by-case basis. The patient's oxygen saturation, heart rate, blood pressure, and urine output should be followed closely. Every patient with NVUGIB needs to have two large bore intravenous lines (18 gauge or larger), or a central venous line catheter if two large bore lines cannot be placed.[27–29] Intravenous fluid resuscitation should follow obtaining venous access. There is no consensus on the amount and type of intravenous fluids, although previously it has been shown that there is no difference in colloids compared to crystalloids in reducing mortality.[30]

Blood transfusion is critical in resuscitation of patients with NVUGIB. It allows adequate oxygenation and tissue perfusion throughout the body to maintain basic cell function. In recent years, there has been controversy and debate over liberal versus conservative transfusions strategies in NVUGIB. Experts suggest aiming for a hemoglobin level above 7 g/dL in patients with no significant comorbidities and above 9 g/dL for patients with ongoing bleeding and known cardiovascular diseases.[20,31,32] The landmark study by Villanueva et al.[33] scrutinizing different hemoglobin levels as a goal for transfusion showed better outcomes and decreased mortality in patients that had lower goals for transfusion (7 g/dL versus 9 g/dL). However, the authors did not include patients with massive exsanguinating bleeding (requiring transfusion prior to randomization), or significant past history of cardiovascular diseases. We suggest that decision for blood

transfusion should be made on an individual basis based on patient's hemodynamic assessment. Platelet transfusion should be performed when platelet count falls below 50×10^9/L.

Proton pump inhibitors (PPI) are the standard therapy and all patients with suspected NVUGIB should be started on intravenous PPI therapy. PPIs work by inhibition of gastric acid secretion by blocking gastric H,K-ATPase. PPIs not only heal ulcerations, but allow for improved platelet aggregation and clot development by raising gastric pH.[34] Current guidelines recommend administration of an initial intravenous PPI bolus of 80 mg followed by 8 mg/h, which has shown to downgrade the lesion at the time of endoscopy.[20,21,35] However, recent studies have shown comparable outcomes in intermittent dosing (80 mg IV, followed by 40 mg IV every 12 h) of PPI versus continuous infusion (80 mg IV, followed by 8 mg/h).[36] Anti-Histamine-type II blockers (H2) are considered inferior to PPI and should only be used if an allergy is present or there is contraindication to PPI use.[20,21]

Prokinetic agents should be considered in large volume NVUGIB. Intravenous erythromycin should be given 20–90 minutes prior to endoscopy.[20,35] Erythromycin improves gastric visualization and decreases the need for repeat endoscopy.[37,38] However, use of prokinetic agents do not affect blood product administration, length of stay, or need for surgery.[39] Guidelines recommend only using erythromycin when large amounts of blood is suspected in the gastrointestinal tract.[20,35] Metoclopramide has currently not been studied enough in the setting of GIB, and the side effect profile is considered more harmful.

Nasogastric lavage was previously recommended due to removing copious amounts of blood that would obscure view during endoscopy, but recently this has fallen out of favor. Nasogastric lavage does not influence need for future transfusion, length of stay, or mortality.[40] Nasogastric lavage has also been shown to be inferior to erythromycin for visualization during endoscopy.[41]

It is important to assess if patients presenting with GIB are on antiplatelet or anticoagulation therapy. Managing patients on these medications can be challenging. Thus, decisions should be made in an interdisciplinary fashion including cardiology, neurology, vascular surgery, or other involved subspecialties. Anticoagulation is needed for diseases such as atrial fibrillation, mechanical heart valves, pulmonary emboli, or deep vein thrombosis. Studies have shown that the upper gastrointestinal tract is the most common site of bleeding in most of these patients.[42–44] In clinically significant NVUGIB, the anticoagulation status should not delay endoscopy.[45]

The main anticoagulant medications are broken down into two groups which are the vitamin K antagonists (VKAs): warfarin and non-vitamin K antagonist oral anticoagulants (NOAC) that inhibit thrombin: dabigatran or inhibit factor Xa: rivaroxaban and apixaban. For patients on warfarin, the ASGE recommends INR to be < 2.5 prior to endoscopic intervention, but one study has shown no difference in rebleeding when the INR is < 4.0 compared to 2.0–3.9.[46,47] Another study by Shingina showed that INR did not predict rebleeding rates.[48] Normalizing the INR only delays definitive endoscopic therapy. If warfarin needs to be reversed, it should be held and 4-factor prothrombin complex concentrates (PCC), which contains factors II, VII, IX, and X (Kcentra) or 3-factor PCC and a low dose of recombinant factor VIIa, need to be given.[49,50] Kcentra should be the initial therapy, rather than fresh frozen plasma, in patients who are predisposed to becoming volume overloaded.[51] When giving vitamin K as a reversal agent, several days are require for the patient to become therapeutically anticoagulated once again, during which time they have a higher thromboembolic risk.[52] Several studies have shown resuming warfarin after endoscopy decreases thromboembolic risk and all-cause mortality and increases risk of bleeding.[53–55]

There is currently conflicting data as to whether the NOACs cause more bleeding than the VKAs.[56–58] Although, studies have shown apixaban is the only NOAC that is not associated with an increase in GIB.[42,59] The other NOACs: dabigatran, rivaroxaban, and edoxaban have shown to increase the risk of acute GIB compared to warfarin.[60–62] Currently, there are no specific guidelines on reversal of NOAC therapy in acute GIB. Dabigatran is the only agent at this time with a specific reversal agent, idarucizumab. In cases of bleeding, dabigatran can also be removed with hemodialysis, but would not be beneficial for the other NOACs which are not cleared through the renal system.[63]

Patients that have with cardiovascular disease are often on antiplatelet agents. The most commonly used antiplatelet medication is aspirin, and patients with recent cardiovascular stents are

usually on dual antiplatelet therapy (DAPT). DAPT includes Aspirin with usually a $P2Y_{12}$ ADP receptor blocker (clopidogrel, ticagrelor, and prasugrel). The American Society of Gastrointestinal Endoscopy (ASGE) recommends holding these medications in serious NVUGIB along with concurrent discussion with other specialists.[46] The COGENT trial suggests starting patients on omeprazole that were on concurrent DAPT.[64] Platelet transfusions can be attempted with patients on DAPT, but may not be very effective.[51] DAPT should be reinstated once hemostasis has been achieved.[45,65]

Endoscopy

Endoscopy is considered the gold standard for diagnosis and treatment of NVUGIB. Endoscopy is recommended within 24 hours of presentation, after appropriate stabilization and resuscitation has been completed.[20,21] Endoscopy within 24 hours has been shown to decrease hospital stay length, reduce risk of rebleeding, or need for further surgical intervention.[66] There are currently several different treatment modalities available to the endoscopist including injection therapy, hemoclips, thermal coagulation, fibrin sealant, and hemostatic powder. The most commonly used forms of endoscopic intervention are thermal coagulation and hemostatic clips.[67,68]

Peptic ulcers are described using the Forrest classification on endoscopy:[69]

- Ia (arterial or spurting hemorrhage)
- Ib (oozing hemorrhage)
- IIa (non-bleeding visible vessel)
- IIb (adherent clot)
- IIc (flat pigmented spot)
- III (clean ulcer base)

Guidelines recommend exposing the ulcer bed for overlying blood clots with thorough irrigation to identify the underlying ulcer.[20,32] Endotherapy is recommended for Forrest class Ia to IIb lesions.[20,68] No endoscopic intervention is recommended for Forrest class IIc and III lesions, but can be treated with oral PPI.[20] Significant recurrent bleeding is rare from Forrest class IIc and III lesions.[70]

Epinephrine is a modality that has been used for several decades. Epinephrine causes local tamponade and vasoconstriction when injected into the mucosa.[71] Epinephrine is usually diluted down to different concentrations, then 0.5–2 ml are injected around 4 quadrants at the site of bleeding. Epinephrine injection has been found to be inferior as a monotherapy and should be used as a combination therapy with hemoclips or thermal coagulation.[67,72]

Endoscopic hemoclips can be used on tears, ulcers, and perforations. They come in varying sizes, shapes, repositioning, and rotation abilities. The hemostatic effect occurs by tissue compression and when needed, apposition, in the cases of tears. One study has shown comparable efficacy to thermal coagulation, but further studies need to be conducted.[72] They have been successful used in Mallory–Weiss tears, Dieulafoy's lesions, and perforations.[73–75]

Thermal coagulation functions by two electrodes at the tip of the probe compressing the vessel initially, followed by application of heat. They can be found as monopolar/bipolar/multipolar or heater probe devices. Bipolar and multipolar are considered safer compared to monopolar probes.[76] Thermal coagulation has been found to be effective in most cases of NVUGIB.[77]

Argon plasma coagulation (APC) is considered non-contact thermal coagulation. It functions by sending an electrical current through ionized argon gas at the tip of the probe. It subsequently heats up and is able to coagulate nearby structures. APC is ideal for superficial vessels such as angiodysplasia and gastric antral vascular ectasia (GAVE). It provides immediate and long-term hemostasis for angiodysplasia.[78]

Hemospray is an inorganic powder that is sprayed endoscopically onto the lesion forming a barrier which promotes thrombus formation and decreases coagulation time.[79] After hemostasis has occurred, the powder is sloughed off regularly within 24 hours.[80] It can be used on a variety of lesions including tumors.[81]

Data is currently insufficient in recommending one modality completely superior to the others. Further studies need to be conducted. The choice of endoscopic usually depends upon characteristics of the lesion, operator experience, and endoscopic modalities available. Newer and future directions of endoscopic therapy include over-the-scope clips (ulcers and spurting vessels), radio-frequency ablation, cryotherapy, and endoscopic suturing.[82]

Endovascular therapy

Transcatheter arterial embolization (TAE) was first used in 1972 as an alternative to surgical management of GIB that failed endoscopic therapy.[83] Since then, there have been several innovations in the field of endovascular therapy. TAE is generally sought after failure of endoscopic therapy with simultaneous use of intravenous PPI therapy.

The classic patient presents with massive GIB with significant hemodynamic compromise, unsuccessful medical management (PPI and resuscitation), and unsuccessful attempts at endoscopic treatment.[84] Endovascular therapy for NVUGIB is mostly centered on the celiac and superior mesenteric arteries and their respective branches. The left gastric artery which branches from the celiac artery provides blood to the distal esophagus and the fundus of the stomach. The gastroduodenal artery provides blood to the gastric antrum and proximal duodenum. The superior mesenteric artery provides blood to the rest of the duodenum through pancreaticoduodenal anastomoses.

TAE is most commonly performed by interventional radiologists in the United States. The common femoral artery is accessed and subsequently different sized guidewires and microcatheters are introduced until they reach the celiac artery.[85] Active GIB is identified by contrast extravasation into the bowel lumen which is positive in up to 61% of ongoing GIB.[85–87] If the site of bleeding cannot be recognized, blind embolization can also be performed. Prior studies have shown no difference in outcomes in patients with or without contrast extravasation during embolization.[84,88] During an esophagogastroduodenoscopy (EGD), an endo-clip can sometimes be placed close to the arterial bleed which helps to locate the approximate artery for selective embolization. Vasopressin was previously used due to its vasoconstrictive properties, but this therapy fell out of favor since it required 12–48 hours of continuous infusion until the bleeding ceased.[85] The advent of embolization greatly expedited the process and has replaced the use of vasopressin over the past two decades.

Due to several endovascular therapies arising in the past few decades, selection depends on operator ease, experience, and availability of equipment. The operator must also ensure that the therapy is simple, precise, and efficacious due to the hemodynamic instability that patients will usually present with. Coils are the most commonly used embolic agent. The advantages are the simple nature; the different lengths, shapes, and materials available; concurrent fluoroscopic visualization during placement; and distal vascular preservation.[85,89,90] Coils with thrombogenic fibers are used to further expedite the occlusion of the targeted vessel. Many coils are now are detachable, if placement is inadequate.[85,88,90] The main disadvantage is that coil deployment is dependent upon coagulopathy and vessel diameter.[89] Improving techniques, newer embolic agents, and fewer complications have allowed TAE to replace surgery as the primary treatment NVUGIB that is refractory to endoscopic therapy. Retrospective studies have shown at least similar efficacy in terms of rates of rebleeding, morbidity, and mortality.[91–93]

Surgery

The role of surgery has decreased over the last few decades due to the widespread use of PPI, *H. pylori* treatment, and advances in endoscopy and endovascular therapies. Surgical intervention should be reserved when endoscopic and/or endovascular therapies have failed, and when concurrent indications are present (perforation or malignancy).[94]

Since gastric acid secretion has several physiologic mechanisms, there is a multifactorial approach to decreasing acid secretion including vagotomy, antrectomy, and subtotal gastrectomy. For refractory ulcer disease, subtotal or total gastrectomy is still considered the definitive surgical

treatment. Bleeding gastric ulcers are generally treated with partial gastrectomy, Bilroth I, or Bilroth II reconstruction. Surgical interventions for duodenal ulcers include truncal vagotomy and pyloroplasty or gastrojejunostomy, selective vagotomy and drainage, partial gastrectomy, or highly selective vagotomy.[95] Surgical repairs of duodenal ulcers also vary based on whether the surgery is elective, or urgent (for bleeding and perforation). Bleeding duodenal ulcers are treated with pyloroduodenotomy and a suture is placed at the site of the bleeding vessel. It is then closed with a pyloroplasty and truncal vagotomy.[96] Mallory–Weiss tears can rarely require surgical intervention and require over sewing the laceration with a running suture.[97]

Malignancies without distant metastasis should generally be resected. Dieulofoy's lesions can also be treated with surgical wedge resection and occasionally gastrectomy with the help of clips placed during endoscopy.[17,98,99] The surgical interventions described above have become such a rare occurrence that some surgical training programs no longer have enough cases to teach these procedures due to the preceding therapies providing better outcomes.

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