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Diagnostic and therapeutic approaches for non-variceal upper gastrointestinal bleeding

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Abstract

Upper gastrointestinal bleeding (UGIB) is a common, life-threatening medical condition. Non-variceal causes account for more than 90% of bleeding episodes. Peptic ulcer disease is the most frequent cause of non-variceal UGIB. Patients present with hematemesis and/or melena but hematochezia might be present in patients with severe bleeding. Despite advances in diagnostic and therapeutic methods, mortality remains high in the elderly and patients with comorbidities. Endoscopy is the primary procedure that should be performed to identify the etiology of UGIB and for treatment purposes following adequate resuscitation of patients. Early endoscopy (within the first 24 hours) has considerably improved the clinical outcomes. A number of scoring systems are being used in patients with UGIB to identify the risk of complications, rebleeding risk, the need for interventional procedures and the risk of death. The most commonly used scoring tools are the Rockall score, Glasgow-Blatchford score and AIMS65 score. Primary treatment modalities include adequate resuscitation, intravenous fluid support, transfusion of red blood cell suspension, acid suppression therapy and administration of prokinetic agents. In general, angiography, computed tomography, technetium-99m-labeled red blood cell scintigraphy and capsule endoscopy may be used in patients whose bleeding cannot be detected endoscopically. Interventional radiological procedures should be initially performed for hemorrhages that cannot be stopped endoscopically and surgical options should be considered when interventional radiological procedures are out of reach or unsuccessful.

Keywords: upper gastrointestinal bleeding, endoscopy, scintigraphy, non-variceal bleeding

1. Introduction

Upper gastrointestinal bleeding (UGIB) is a common, life-threatening medical condition. UGIB is defined as bleeding originating from a source proximal to the ligament of Treitz including esophagus, stomach and duodenum. UGIB is broadly divided into two groups as variceal and non-variceal hemorrhages. Gastroduodenal ulcers are the leading cause of non-variceal UGIB (Hunt et al., 1995). Non-variceal causes account for more than 90% of bleeding episodes. Clinically, it may present with massive bleeding as well as slow, chronic bleeding. Despite the advances in diagnostic and therapeutic methods, bleeding-related mortality has not changed significantly in comparison to previous years because the mortality is still high in the elderly and the patient population with comorbidities (Wilcox and Clark, 1999; Hwang et al., 2012). In Western countries, the reported annual incidence of UGIB in adults ranges from 103 to 172 episodes per 100,000 population (Rockall, et al., 1995; Van Leerdam et al., 2003). Hospitalizations for UGIB have decreased by nearly 20% in the last decade due to reduction of peptic ulcer bleeding as a result of the use of anti-secretory drugs and decreased prevalence of *Helicobacter pylori* (Laine, et al., 2012). The mainstay of patient management is achieving hemodynamic stability, followed by performing endoscopy for the purposes of diagnosis and treatment. Early endoscopy within the first 24 hours have greatly improved clinical outcomes (Vergara, et al., 2014). In 80% of the cases, non-variceal UGIB stops spontaneously (Van Leerdam et al., 2003). At the same time, early risk stratification of patients is important for treatment planning including the timing of endoscopic treatment and Glasgow-Blatchford, Rockall and AIMS65 scores are commonly used for this purpose (Alzoubaidi, et al., 2019). In the case of persistent and recurrent bleeding, repeat upper endoscopy should be performed initially, followed by consideration of interventional radiology procedures such as trans arterial chemoembolization (TACE) and surgical treatment options (Gralnek et al., 2015).

2. Etiology of non-variceal upper gastrointestinal bleeding

The etiology of non-variceal UGIB most commonly involves peptic ulceration/inflammation (most prevalent, approximately 50%), vascular lesions, congestive gastropathy, malignant

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lesions and other causes (Mallory-Weiss tears, Cameron ulcers, anastomotic ulcers, post-procedural hemorrhages). The etiology cannot be determined in about 10% of the patients (Table 1) (Naseer et al., 2020).

Table 1. Causes of non-variceal gastrointestinal bleeding

Ulcer / Inflammation	Peptic ulcer disease Esophagitis, gastritis, duodenitis Anastomotic ulcers
Vascular Lesions	Gastric antral vascular ectasia (GAVE) Dieulafoy lesion Angiodysplasia Aorta-enteric fistula
Congestive Gastropathy	Portal hypertensive gastropathy
Malignancies	Gastric, esophageal tumors Metastatic tumors
Other	Mallory Weis tear Cameron ulcer

Peptic ulcer disease is defined as a lesion that penetrates into the muscularis mucosa layer of the gastric and duodenal mucosa and is the most common cause of UGIB. *Helicobacter pylori* infection, the use of non-steroidal anti-inflammatory drugs, physiological stress and increased gastric acid secretion are risk factors for bleeding (Hunt et al., 1995). Esophagitis is a frequent cause of UGIB and its risk factors include gastroesophageal reflux disease, the use of certain medications and infections (Da Costa et al., 2001; Guntipalli et al., 2014). Gastritis and duodenitis are inflammation-mediated mucosal injuries and although these are frequent endoscopic findings, they are less likely to cause hemorrhage and usually self-limiting (Guntipalli et al., 2014).

Vascular lesions of the gastrointestinal tract that may cause UGIB to include angiodysplasia, Dieulafoy's lesion and gastric antral vascular ectasia (GAVE). Angiodysplasia is the most common vascular abnormality of the gastrointestinal tract. In the upper GI tract, angiodysplasias are mostly found in the stomach, duodenum but rarely in the esophagus. Its pathogenesis has not been fully elucidated. Endoscopic diagnosis of angiodysplasia can sometimes be challenging because the lesions are small and may resemble fresh bleeding. Rarely, the diagnosis of angiodysplasia can be made by radiological or surgical modalities. Dieulafoy's lesion is a vascular abnormality consisting of dilated, aberrant submucosal vessels and an infrequent cause of UGIB. The majority of the lesions are located in the stomach. Dieulafoy's lesions exhibit an intermittent bleeding pattern and therefore, are identified at a low rate on initial endoscopic examination (Marangoni, et al., 2009). GAVE also known as 'watermelon stomach' is a rare but important cause of UGIB. Endoscopically, it is characterized by linear, diffuse erythematous stripes that radiate from the pylorus to the antrum, giving the appearance of watermelon streaks. The etiology of GAVE is not clear (Jabbari et al., 1984). Mallory-Weiss syndrome is marked by longitudinal superficial mucosal lacerations (Mallory-Weiss tears). Mallory-Weiss tears are often located in the gastroesophageal junction and may extend proximally to involve the stomach and duodenum. Excessive alcohol consumption is the most common cause. Risk factors include hiatal hernia, hyperemesis gravidarum and gastroesophageal reflux disease. Repeated acts that cause a sudden and severe increase in the intra-abdominal pressure such as retching and vomiting precipitate Mallory-Weiss syndrome. Longitudinal tears may progress and extend deep into submucosal arteries and veins, causing bleeding. Bleeding is often self-limiting and recurs infrequently (Kortas, et al., 2001; Rawla and Devasahayam, 2019). Gastrointestinal tumors, primary gastrointestinal tumors, metastatic tumors and locally invasive tumors may cause UGIB. Gastric tumors are the most common cause of UGIB (Kim and Choi, 2015). Unlike other non-variceal UGIB, the success rate of endoscopy is low in bleeding from gastrointestinal tumors and rebleeding after a short time occurs in about 80% of the cases. Surgical or radiological intervention may be required when the endoscopic procedure fails (Adler et al., 2004).

3. Diagnostic and therapeutic approaches for the management of bleeding

There have been considerable advances in the management of UGIB in recent years. However, advanced age and comorbid conditions are still risk factors for many patients (Lanas, 2010) The management of bleeding consists of 3 approaches: pre-endoscopy, endoscopy, and post-endoscopy. For treatment planning, it is important to question the presence of comorbidities (coronary artery disease, pulmonary disease, renal disease, heart failure, chronic liver disease). It allows identification of thresholds for transfusion of red blood cell suspension and intravenous fluid support. History of medication use (non-steroidal anti-inflammatory drugs, antiplatelet drugs, anticoagulants) is crucial in terms of the balance between bleeding control and cardiovascular risk as well as to determine whether the medication should be discontinued and when it should be resumed. Studies have shown that routine nasogastric intubation does not offer any clinically relevant benefit for patients. The presence of coffee ground material or fresh blood in the nasogastric content indicates UGIB (Lanas, 2010). A number of scoring systems are being used in patients with UGIB to identify the risk of complications, rebleeding risk, the need for interventional procedures and mortality risk. These scoring systems are categorized into three groups as those including endoscopic parameters, those with both clinical and endoscopic parameters and those with clinical parameters alone. It is recommended that these scoring tools be used in an early stage in patients presenting with UGIB (Barkun et al., 2010). The most widely used scoring systems are Forrest classification, Rockall score, Glasgow-Blatchford score and AIMS65 score.

3.1. Initial resuscitation

For a patient with a preliminary diagnosis of UGIB, the first thing to do is to assess the patient's airway, breathing and circulation. Oral intake of the patient is stopped. Adequate peripheral access should be achieved with two large-bore (18

gauge) catheters and a central venous catheter inserted when necessary. Blood pressure, oxygen saturation and heart rate should be monitored. Patients should be provided intravenous fluid support without delay. It is particularly important to ensure hemodynamic control and stabilization with intravenous fluid support prior to endoscopy; this way, the risk of treatment-related complications is reduced (Baradarian et al., 2004). No difference in mortality was observed in a meta-analysis comparing colloids and crystalloids for fluid resuscitation in critically ill patients (Perel and Roberts, 2012). The quantity of fluid to be administered is adjusted according to the hemodynamic state of the patient.

3.2. Anemia and thrombocytopenia

In patients with UGIB, red blood cell (RBC) transfusion is often required to maintain tissue perfusion. The decision for transfusion is made individually on a patient basis. Hemoglobin threshold for transfusion is a controversial topic. In hemodynamically unstable patients and patients with severe bleeding, transfusion up to higher thresholds is needed, as hemoglobin values will decrease even further with intensive fluid treatment. Reduced transfusion volume is associated with decreased mortality in hemorrhagic patients; this has led to the consideration of the negative effects of over transfusion on hemostasis (Crooks et al., 2011). Transfusion of red blood cell suspension is needed in patients with active hemorrhage regardless of hemoglobin level. The liberal transfusion strategy aims transfusion to patients with hemoglobin values below 9-10 g/L, whereas the restrictive transfusion strategy targets the patient population with hemoglobin values below 7-8 g/L. In a meta-analysis, patients treated with the restrictive strategy had lower rates of mortality and rebleeding in comparison to patients treated with the liberal strategy (Odutayo et al., 2017). If there is a concern for potential harm to the patient from ischemia (e.g., coronary artery disease) related to anemia, the hemoglobin value is kept above 9 g/L. In the presence of active ischemia, RBC transfusion should be given by keeping the hemoglobin value at 10 g/L. In patients with UGIB, transfusion of platelet suspension is warranted at a platelet count less than 50.000 cells/microliters. There is no evidence demonstrating the benefit of platelet transfusion suspension in patients receiving antiplatelet drugs; therefore, it should be decided on a patient basis.

3.3. Use of antiplatelet and anticoagulant medications

Increasing use of antiplatelet and anticoagulant drugs is a risk factor for UGIB and 44% of patients take these medications (Chang et al., 2015; Dunne et al., 2019). Anticoagulant and antiplatelet drugs are discontinued in UGIB patients when possible. However, potential harms from discontinuation of these drugs should be weighed against the risks of bleeding prior to stopping these therapies and the decision to discontinue or administer an antidote should be made individually for each patient by consulting the departments that started the patient on these medications.

Guidelines suggest an INR (International Normalized Ratio) value less than 2.5 before performing endoscopy (Acosta et al., 2016). Fresh frozen plasma is usually used in patients with a high INR value and prothrombin complex concentrate (PCC) is recommended to achieve a rapid INR reduction in patients with life-threatening bleeding (Maltz et al., 2000). Limited data are available for novel oral anticoagulants (NOACs) which have a short half-life of 5 to 17 hours. PCC may be used in severe bleeding (Veitch et al., 2016). There are no sufficient data on the use of idaricuzimab as an antidote for dabigatran and andexanet alfa (a recombinant modified Factor Xa) for Factor Xa inhibitors in patients with UGIB.

3.4. Acid suppression

Gastric acid suppression contributes to achieving hemostasis. The use of proton-pump inhibitors (PPIs) prior to endoscopy reduces the symptoms of severe bleeding and the need for endoscopic treatment. Patients are started on PPI treatment on the day of admission. Optimal dosage is not clear; studies showed that PPI treatment administered as an intravenous 80 mg bolus dose followed by continuous infusion at 8 mg/h for 72 hours reduced the rates of rebleeding and mortality compared to placebo and non-PPI treated groups (Laine and McQuaid, 2009). Some guidelines recommend intermittent use of high-dose intravenous or oral PPI (80 mg bolus, followed by 80 to 160 mg daily in divided doses) (Gralnek et al., 2015). Patients with peptic ulcer should receive a PPI once daily for 4 -8 weeks after a UGIB.

3.5. Prokinetic agents and tranexamic acid

Prokinetic agents such as erythromycin and metoclopramide improve the endoscopic visibility by accelerating gastric emptying when given prior to endoscopy and they may also reduce the need for a second-look endoscopy. Erythromycin, administered as a single dose at 20-120 minutes before endoscopy, has been shown to provide better endoscopic visibility, shorter duration of endoscopy and reduced need for second endoscopy (Frossard et al., 2002). Tranexamic acid is an antifibrinolytic agent; studies have shown that it has no benefit in the treatment of gastrointestinal bleeding and predisposes to venous thrombus (Roberts et al., 2020).

3.6. Risk Scores

In addition to bleeding, mortality has been shown to be associated with other clinical parameters (e.g., age, comorbidities, shock, endoscopic diagnosis, hemoglobin levels, ulcer diameter, need for transfusion), all of which can have an impact on the prognosis in patients with non-variceal UGIB (Nahon et al., 2012; Monteiro, et al., 2016). The Forrest classification is used to predict the rebleeding risk of patients based on endoscopic findings (Table 2). The most commonly used scoring tool is the Rockall score with both clinical and endoscopic components. Possible scores range from 0 to 11 points.

Table 2. Forrest classification

Forrest Score	Endoscopic Appearance	Risk of Rebleeding (%)
1a	Ulcer with active pulsating bleeding	90
1b	Ulcer with active non-pulsating bleeding	10-20
2a	Ulcer with a visible nonbleeding vessel	50
2b	Ulcer with an adherent clot	25-30
2c	Ulcer with hematin on ulcer base	7-10
3	Ulcer with a clean base without signs of recent bleeding	3-5

Endoscopic findings are not included in the calculation of clinical Rockall score and scoring is done with maximum seven points (Table 3) (Rockall, et al., 1996). The Glasgow-Blatchford score (GBS) consists of eight clinical and laboratory parameters. Scores range between 0 and 23 points. Higher scores indicate greater need for endoscopy. The major advantage of this scoring tool is its ability to identify low-risk patients who do not need to be admitted to hospital. A patient suspected of having an UGIB whose score is 0 can be safely followed on an outpatient basis (Table 4) (Blatchford, et al., 2000; Stanley et al., 2009).

Table 3. Rockall scoring system

Variable/ Score	0	1	2	3
Age	<60	60-79	80≥	
Shock	No shock	Blood pressure>100 Pulse≥100	Blood pressure<100 Pulse>100	
Comorbidity	None		Circulatory failure/coronary artery disease	Renal failure Liver failure Disseminated malignancy
Diagnosis	Mallory-Weiss syndrome/no pathology	All other diagnosis	Malignancy of the upper gastrointestinal tract	
Endoscopic signs of bleeding	None/dark spot		Blood/adherent clot/visible or spurting vessel	

Table 4. Glasgow-Blatchford scoring system

Variable	Score
Blood urea nitrogen (mmol/L)	
6.5-8	2
8-10	3
10-25	4
>25	6
Hemoglobin for men (g/L)	
120-130	1
100-120	3
<100	6
Hemoglobin for women (g/L)	
100-120	1
<100	6
Systolic blood pressure (mm/hg)	
100-109	1
90-99	2
<90	3
Pulse≥100	1
Other markers	
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

The AIMS65 score is an acronym of albumin, INR, alteration in mental status, systolic blood pressure and age. It is a clinical risk scoring tool and the score is calculated by assigning one point for each of the aforementioned components (for a total of five scores). The presence of two or more components indicates a higher risk of mortality (Table 5) (Saltzman et al., 2011).

Table 5. AIMS65 scoring system

Variable	Score
Albumin<3 g/dL	1
INR>1.5	1
Systolic Blood Pressure<90 mm/Hg	1
Altered Mental Status	1
Age>65 year	1

3.7. Endoscopy

Endoscopic examination is recommended for UGIB patients within the first 24 hours after admission for diagnostic and therapeutic purposes. This time interval is 12 hours in patients with impaired hemodynamic state and suspicion of variceal bleeding (Sung et al., 2011). Endoscopic treatment should be instituted following adequate resuscitation and hemodynamic stabilization. In patients with a higher risk of mortality and bleeding (GBS≥12), clinical outcomes were not different between those undergoing early endoscopy (within 6-24 hours) and those treated with emergency endoscopy (within 0-6 hours) (Lau et al., 2020). The diagnosis and treatment of UGIB are conducted by endoscopic examination. In general, angiography, computed tomography, technetium-99m-labeled red blood cell scintigraphy and capsule endoscopy may be used in patients whose bleeding cannot be detected endoscopically. The colonoscopic examination is planned to identify colon-related etiologies for patients in whom a bleeding focus cannot be demonstrated by endoscopy.

Epinephrine injections, argon plasma coagulation, heater probe and endoscopic clips are the methods used in endoscopic

treatment. In the case of failure of conventional treatments, over the scope clips, hemostatic powder, endoscopic suture, endoscopic band ligation, coagrasper or hemostatic forceps, endoscopic ultrasound-guided angiography, cryotherapy, radiofrequency ablation and endoscopic laser coagulation are newer treatment modalities that can be used in UGIB (Naseer et al., 2020). Firstly, repeat endoscopy should be done in a recurring UGIB episode. Interventional radiological procedures should be initially performed for hemorrhages that cannot be stopped endoscopically and surgical options should be considered when interventional radiological procedures are out of reach or unsuccessful. The transarterial chemoembolization (TACE) procedure is recommended for bleeding that persists after optimal endoscopic treatment (Gralnek et al., 2015).

4. Conclusion

Currently, non-variceal upper gastrointestinal bleeding is still a common condition. There have been considerable advances in the endoscopic treatment modalities in the last decade. It is important to determine the risk score of the patients in an early stage. Patients should be evaluated and managed thoroughly taking into account all aspects of their condition due to high numbers of patients with comorbidities, concomitant use of antiplatelet and anticoagulant drugs. Hemostatic powder, over the scope clips, endoscopy guided by Doppler probes are newly developed endoscopic techniques for use in patients in whom bleeding cannot be controlled with conventional endoscopic interventions.

Conflict of interest

All authors declare no conflict of interest regarding this manuscript.

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