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Review

Clinical approach to the patient with acute gastrointestinal bleeding

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Summary. Gastrointestinal bleeding (GIB) is a very common condition at all ages, with high rates of morbidity and mortality, especially in case of acute presentation. The optimal management of acute GIB requires a timely overview of vital signs and clinical presentation to stabilize the patient if necessary and set up the most adequate diagnostic and therapeutic approach, based on the suspected etiology. Endoscopy plays a major role both in diagnosis and treatment of acute GIB, as allows the application of several hemostasis techniques during the diagnostic session, which should preferably be performed within 24 hours from the acute event. The hemostasis technique should be chosen based on type, etiology of the bleeding and the operator preference and expertise. Nevertheless, several challenging cases need the cooperation of radiology especially in the diagnostic phase, and even in the therapeutic phase for those bleedings in which medical and endoscopic techniques have failed. Imaging diagnostic techniques include mainly CT angiography, scintigraphy with labeled erythrocytes and arteriography. This last technique plays also a therapeutic role in case arterial embolization is needed. Only those patients in which the previous techniques have failed, both in diagnosis and treatment, are candidates for emergency surgery. (www.actabiomedica.it)

Key words: gastrointestinal bleeding, hemostasis, endoscopy, videocapsule endoscopy, device-assisted enteroscopy

Background

Gastrointestinal bleeding (GIB) is a very common condition in clinical practice, with an incidence of about 50-150 cases per 100.000 population (1) with high mortality rates up to 5-10% (2, 3). Therefore, it represents a relevant problem for public health, being morbidity and mortality rates still high, despite continue ameliorations in medical and endoscopic treatment (4). Even though prevalent in adults, gastrointestinal bleeding may present at any age, with an incidence around 6% (5) and highest mortality rates associated with GI bleeding especially in cases with intestinal perforation (8.7%) and esophageal perforation (8.4%) in pediatric age (6).

Overall, gastrointestinal bleeding may have a wide variety of clinical presentations, with different signs, symptoms and severity, therefore a timely and precise diagnostic and therapeutic approach is mandatory to optimize the patient's management minimizing the risk of complications.

Gastrointestinal bleedings can be divided in upper GIB (UGIB) and lower GIB (LGIB) based on the location, which can be proximal or distal to the liga-

ment of Treitz. Among LGIBs, those located in the small intestine have shown to be separated entities from colonic bleeding, in terms of etiology, and accessibility and can be defined middle GIB (MGIB) (7).

Moreover, GIB can be defined acute if as being of recent duration (arbitrarily less than 3 days) and might cause instability of vital signs, anemia and/or the need for blood transfusion, or chronic in case the blood loss lasts for several days with an intermittent and slow evolution (7). Besides, GIB is defined obscure in case the bleeding of unknown origin that persists or recurs after negative findings on initial evaluation using bidirectional endoscopy (5).

The aim of the present review is to focus on acute GIB with a practical clinical approach.

Initial evaluation

Acute GIB may present as a clinical emergency, therefore priority is represented by vital signs evaluations, respiratory and circulatory function with hemodynamic resuscitation if necessary (8). Firstly, ventilation must be guaranteed either with non-invasive (aspiration of secretions, blood or vomit) or invasive methods (oro-tracheal intubation, cricothyrotomy or tracheotomy) to protect the patient against aspiration pneumonia. In parallel, the eventual status of hemorrhagic shock must be checked, with the evaluation of blood pressure, temperature, cardiac and respiratory frequency. Furthermore a venous access must be prepared to adequately provide for fluids and/or blood transfusion to reach a hemoglobin concentration of approximately 7 to 8 g/dL, administer eventual medications and to take blood samples (7, 8). Early intensive hemodynamic resuscitation of patients with acute GIB has been shown to significantly decrease mortality (9). Nevertheless, aggressive resuscitation with blood products and crystalloid should be avoided as it theoretically can increase portal pressures, leading to increased risk of rebleeding and mortality (8).

Hypovolemia and the grade of severity of anemia present with recognizable signs. In case of mild hypovolemia (loss <15% of the total blood volume) the patient presents with tachycardia, tachypnea, pallor, low temperature and augmented capillary refill time. In case of moderate and severe hypovolemia the patient presents with orthostatic hypotension (orthostatic blood pressure drop >10 mmHg), central hypoperfusion signs including lethargy and coma, oliguria and hyperlactacidemia (9).

History and clinical examination

Once the patient is stabilized, an accurate history must be made with the aim to identify specific signs of gastrointestinal bleeding and other conditions predisposing to hemorrhage. Among the most typical signs of GIB we recognize hematemesis, melena and hematochezia.

Hematemesis consists in the emission of blood in concomitance with vomit; blood can be either bright red or brown, based on the length of permanence in contact with chloridric acid in the stomach. Melena consists in the passage of dark tarry stools with characteristic smell due to the transformation of hemoglobin into hematin by intestinal microbiome and digestive enzymes; melena may present in case of upper, lower GIB or middle GIB, even though it is a manifestation of distal lower GIB only if the transit is very prolonged (paralytic ileus) (7). Hematochezia consists in the emission of bright red during evacuation, while proctorrhage is the passage of bright red independently from evacuations. Hematochezia and proctorrhage are more typical of LGIBs from left colon, rectum of anus, although rarely the may present in case of UGIB due to accelerated transit and/or severe bleeding (7, 10). Clinical evaluation should be also focused on conditions predisposing to hemorrhage. Firstly, localization of bleeding other than the gastrointestinal tract should be excluded, such as nasal, pharyngeal, laryngeal and bleeding from the respiratory tract, which can mimic GIB due to the emission of swallowed blood from these areas. Hepatic disease as a possible cause of portal hypertension and coagulopathy should be investigated. Moreover, accurate medication history should be carried out, with attention to the assumption of anticoagulants, antiplatelets, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or corticosteroids (4). Coagulopathy (defined as an international normalized ratio of prothrombin time >1.5) underlying GIB is a

frequent and adverse prognostic factor and can be associated to thrombocytopenia (<50,000 platelets/μl). They should be treated with fresh frozen plasma and platelet transfusion respectively (8). Anyway, the treatment of coagulopathy is not yet precisely established, both with regards to the INR threshold which should be reached (1.5-1.8), and to the optimal transfusion which should be administered (fresh frozen plasma, vitamin K to reverse AVK drugs, prothrombin complex) (7, 8). Also volume replacement presents several therapeutic options, remaining the preference of crystalloids over colloids a matter of debate (7). An accurate clinical examination should be also directed to research for signs pathognomonic of underlying diseases e.g. anal lesions could suggest the presence of Crohn disease, or the typical peroral pigmentation could be suggestive for Peutz-Jeghers syndrome. Moreover, clinical examination could highlight eventual painful regions to better direct the consequent diagnostic approach, which should be always directed based on the suspected underlying cause.

Upper acute GI bleeding

Upper GIB can be divided into variceal and non-variceal bleeding. The first category is consequent to portal hypertension and formation of esophageal and gastric varices, while the second one is comprehensive of all other possible causes of bleeding. Details are shown in Table 1.

In accordance to US registries, peptic ulcer is the most frequent cause of UGIB, representing up to 27-40% of cases in adult population (11). Peptic ulcer is frequently associated to Helicobacter pylori infection, whose prevalence is still high among western countries populations up to 22-48% and eradication rates not yet satisfactorily (12, 13). Duodenal ulcers are usually more frequent than gastric ulcers, even though the bleeding risk is comparable and consequent to an arteriolar erosion at the base of the ulcer (11). Risk factors for bleeding peptic ulcer due to Helicobacter pylori infection include NSAIDs use, alcohol intake and renal failure (14). NSAIDs may cause gastric and duodenal

Table 1. Main etiologies of acute upper gastrointestinal bleeding

Upper gastrointestinal bleeding: Main etiologies		
Variceal	Non-variceal	
	Primary	Secondary
- Rupture or bleeding of esophageal varices	- Mallory-Weiss Syndrome	- Gastric or duodenal ulcer (e.g. Helicobacter pylori ulcer)
- Rupture or bleeding of gastric varices	- Boerhaave Syndrome	
- Hypertensive gastropathy (GAVE)	- Peptic esophagitis	- Gastritis due to drugs (e.g. NSAIDs)
	- Esophageal benign or e malignant tumors	- Gastritis due to caustic ingestion
	- Gastric or duodenal idiopathic ulcer	- Post-mucosectomy/submucosectomy bleeding
	- Gastric benign or e malignant tumors	- Hemobilia post ERCP
	- Angiodysplasias	- Anastomotic bleeding
	- Rendu-Osler-Weber Syndrome	
	- Aorto-enteric fistulas	
	- Dieulafoy lesion	

ulcers independently from other predisposing factors, by inhibiting COX-mediated prostaglandins synthesis, which are well known protective factors for the gastrointestinal mucosa. It is esteemed that daily use of NSAIDs can increase the risk of developing duodenal ulcer up to 40 times (5). Among bleeding lesions associated to episodes of vomit, Mallory-Weiss Syndrome and Boerhaave Syndrome are described. The first one consists in a linear lesion of the gastro-esophageal junction mucosa and represents around 15% of cases of UGIB, while the second one consists in a transmural lesion and is quite rare. Dieulafoy lesion is a vascular anomaly, characterized by the presence of a tortuous artery with augmented diameter, located in the submucosal layer of the gastrointestinal tract. This clinical condition is rare, with an incidence of 5% for all causes of GIB.

More rare causes of UGIB include aorto-enteric fistula, due to the erosion of the aortic wall which flows into the gastrointestinal lumen; the most frequently interested area is the II-III duodenal tract. Angiodysplasia of the upper GI tract represent 2-4% of cases of UGIB and are consequent to vascular abnormalities and enlargement of mucosal and submucosal vessels (15). Among iatrogenic UGIB are of note post-mucosectomy or post-submucosectomy bleedings. This complication can occur in up to 3.7% of cases and should be always considered particularly after asportation of large lesions >2cm of diameter, and in patients under antiplatelet or anticoagulant treatment (16).

Anastomotic bleeding after major surgery of the gastrointestinal tract is a rare but potentially life-threatening complication, occurring in up to 2% of cases (17).

Lower and middle acute GI bleeding

Although a patient presenting with hematochezia is strongly suspected for having a LGIB, often it is difficult to predict and understand location, etiology and severity of the bleeding at the moment of clinical presentation. A variable proportion from 10% to 20% of patients with suspected LGIB, result having an upper or middle source of bleeding and in 10% of cases the source remains unidentified. Lower GI bleeding represents around 20-30% of all GIB. Annual incidence in USA is esteemed to be around 20-27 cases per 100.000 populations, while in Europe it is esteemed to be of about 9 cases per 100.000 populations (18). Main etiologies are shown in Table 2.

As for UGIB, the causes of LGIB are numerous and can vary greatly in terms of severity, mortality and population more frequently interested. Recent prevalence data show that the most frequent cause of acute LGIB is diverticular bleeding (30-65% of cases), followed by bleeding angiodysplasias (4-15% of cases), hemorroidal bleeding (4-12%), ischemic colitis (4-11%), inflammatory colitis including Inflammatory Bowel Diseases (IBD) (3-15%), polyps and umoral bleeding (2-11%), post mucosectomy/submucosectomy (2-7%), rectal ulcer (0-8%) (19).

Furthermore, an infectious colitis should always be excluded in case of acute diarrhea mixed with blood. The most common etiologic agents are Salmonella, Shigella, Campylobacter, Yersinia enterocolitica, Clostridium difficile, Escherichia Coli (0157: H7), Entamoeba Histolitica and should be searched on stool cultures. Also for LGIBs and middle GIBs, NSAIDs play a major role in causing hemorrhage, as their mechanism of action can provoke ulcers throughout the whole gastrointestinal tract, in particular, NSAIDs assumption is related to bleeding colonic diverticula (19, 20). Ischemic colitis is the etiology in 9–24% of all patients hospitalized for acute lower gastrointestinal bleeding (21). It is rare in children with CI are only rarely reported, but CI occurs in adults of all ages

Table 2. Main etiologies of acute lower and middle gastrointestinal bleeding

Lower and middle gastrointestinal bleedings: Main etiologies
- Complicated diverticulosis
- Angiodysplasias
- Ischemic colitis
- Inflammatory Bowel Diseases
- Benign and malignant tumors
- Post mucosectomy and submucosectomy bleeding
- Solitary Rectal ulcer
- Dieulafoy lesion
- Hemorrhagic Enterocolitis (e.g. infectious, NSAIDs induced)
- Vasculitis (e.g. Schonlein-Henoch purpura)
- Meckel diverticulum

and increases with age, especially after the age of 49 years. Ischemic colitis is consequent to alterations in the systemic or mesenteric circulation, even though it is believed that local hypoperfusion and reperfusion is the main cause of the injury (21).

Of all the sources of GI bleeding, only a small percentage (5%) is attributed to small-bowel sources. Among the main etiologies of middle GIB Angiodysplasias of the small bowel account for 20% to 30% of small-bowel bleeding and are more frequent in older patients. Small-bowel tumors (eg, GI stromal tumors, carcinoid tumors, lymphomas, and adenocarcinomas) should also be considered, as they can present with small-bowel bleeding in both younger and older patients (22).

Diagnosis of acute GIB

Diagnostic endoscopy

The diagnostic gold standard of GIB is represented by endoscopy, which should be performed within 12-24 hours from the event, to optimize the management of the patient, not only providing a diagnosis, but also permitting hemostasis at the same time (8). The correct timing of endoscopy is of paramount importance to improve patient's outcomes, including hospital stay and the assessment of the risk of rebleeding (8). Based on signs, the diagnostic approach is started either by esophagogastroduodenoscopy (EGDS) or colonoscopy. All endoscopic procedures should be performed only once the patient is stabilized, and with a continuous monitoring of ECG and vital parameters. In case of UGIB an EGDS should be promptly performed, to allow direct visualization of gastrointestinal mucosa until distal duodenum. With regards to the assessment of rebleeding risk, in case a non-variceal etiology is individuated, it is recommended to apply the Forrest classification, which aims to identify patients at risk of persistent ulcer bleeding, rebleeding and mortality. Forrest classification is defined as follows: FIa spurting hemorrhage, FIb oozing hemorrhage, FIIa nonbleeding visible vessel, FIIb an adherent clot, FIIc flat pigmented spot, and FIII clean base ulcer (23). In case a variceal bleeding is identified, endoscopy allows a morphologic evaluation and localization of varices, which is necessary to set up a therapeutic decision and/or a follow up (24).

Most importantly, EGDS not only allows a prompt and precise identification of the bleeding source proximal to the ligament of Treitz, but also allows timely hemostasis (see paragraph "endoscopic therapy"). Patients presenting with hematochezia and concurrent hemodynamic instability should be firstly evaluated by EGDS to exclude an upper gastrointestinal bleeding source. Otherwise, ileo-colonoscopy is recommended as the first step in the evaluation of acute LGIB, being the diagnostic yield high up to 89–97% (7). The optimal timing of ileo-colonoscopy after initial presentation ranges from 12 h to 48 hours. As well as EGDS, colonoscopy can determine the source and type of bleeding, and helps identifying patients with ongoing bleeding or those who are at high risk of rebleeding, moreover, allows endoscopic hemostasis if necessary. Unlikely EGDS, ileo-colonoscopy requires thorough cleansing of the colon even in acute LGIBs, to improve sensitivity and safety of the procedure by decreasing the risk of perforation. Although in urgent procedures it is not always possible, an optimal purge of the colon consists in the assumption of 3–6 litres of a polyethylene glycol-based solution, anyway patients generally tolerate consumption of 1-2 l per hour (7). In case of negative upper and lower endoscopy and presence of GIB, the small bowel should be investigated. Usually, the exploration of the small intestine is elective and performed by using firstly Video Capsule Endoscopy (VCE), then by performing device-assisted enteroscopy (DAE) in case an operative endoscopic intervention is needed (22). This last technique, which encompasses Balloon-assisted enteroscopy (BAE) and Push-enteroscopy, is certainly more complex than VCE, has lower availability among Endoscopic Centers and should be performed in trained tertiary-care centers. In multiple large studies of patients with small-bowel bleeding who underwent BAE, the diagnostic yield ranged from 43% to 81%, and rates of treatment success ranged between 43% and 84% (22).

Imaging

Because of the multitude of pathologic processes that provoke GI bleeding, and its often intermittent na-

ture, imaging can be applied in case of negative upper and lower endoscopy and/or in case of contraindications for endoscopy (25). Computed Tomography (CT) is a readily available imaging method in the emergency departments of most hospitals. CT should always be applied with intravenous contrast, especially in case of GI bleeding, when contrast material extravasation can be revealed with rates of less than 0.4 mL/min. However, contrast-enhanced CT has limited utility in cases of intermittent hemorrhage and involves intravenous contrast material and a relatively high radiation dose, therefore this technique should always be used in case of active hemorrhage: studies demonstrate that the CT sensitivity reaches rates of 91%-92% in case of active hemorrhage, while shows lower values in case of obscure GIB, down to 45%-47% (25). Visceral arteriography is also used to typically identify active bleeding, when the rate is at least 0.5-1 ml/min. The specificity of this procedure is 100%, but sensitivity varies from 47% with acute LGIB to 30% with recurrent bleeding. Arteriography should be reserved for patients who have massive bleeding that precludes colonoscopy, or for whom endoscopies were negative. visceral angiography has a complication rate of 9.3% (7). Angiography may be also applied to achieve hemostasis by intra-arterial infusion of vasopressin or arterial embolization via the angiographic catheter. Compared to intra-arterial infusion of vasopressin, transcatheter embolization is a more definitive means of controlling hemorrhage. Nevertheless transcatheter embolization presents rate of bowel infarction ranging from 13 to 33%, therefore its use should really follow precise indications and be chosen after failure of other techniques (2). Nuclear scintigraphy is a sensitive method for detecting gastrointestinal bleeding at a rate of 0.1 ml/min. Compared to angiography, the method is more sensitive, but less specific. The technique mainly applies either technetium sulphur colloid or [99Tcm] pertechnetate labeled red blood cells and localizes bleeding only to an area of the abdomen, until the intra luminal blood is moved away by intestinal motility. When scans are positive within 2 h after injection of the labeled erythrocytes, localization is correct in 95–100% of cases, although accuracy decreases to 57–67%. For longer times. Overall, scintigraphy might be useful, especially for recurrent bleeding, when other methods have failed (2, 7).

Endoscopic therapy

Endoscopic hemostasis is a promptly available technique which can be very often applied directly during the diagnostic exploration. Treatment modalities include injection therapy, the use of mechanical devices such as metallic clips and band ligation, application of hemospray and electrocautery therapy.

The choice depends on the site and the features of the bleeding lesion, the clinician's personal experience with the devices, and access to the bleeding site (7). Injection therapy is based on the use of a needle to inject locally a chemical agent. Injection therapy agents include epinephrine and sclerosant agents. Epinephrine, prepared in 1:10.0000 to 1:20.0000 dilutions, is the most commonly employed agent. Side effects due to first-pass metabolism through the liver are usually low (transient tachycardia and hypertension). Epinephrine can be injected into the submucosa and/or directly into the ulcer base. Typically, "4 quadrant injection" in 0.5 to 2 ml aliquots of 1:10.000 epinephrine is performed within 3 mm of the bleeding vessel (1). Sclerosants agents (sodium monrrhuate, sodium tetradecyl sulphate and ethanol) induce localized thrombosis of the bleeding vessel with consequent hemostasis. Sclerosants are mostly used to treat varices and should be used with caution for colonic lesions given the unpredictable depth of penetration through the thin colonic wall. Risks related to injection therapy include increased bleeding, rebleeding, bowel ischemia and perforation. Mechanical therapy is based on the use of devices like clips and band ligation (the last one is mostly used for variceal bleeding), alone or combined with other techniques. Endoscopic clips directly tampon the bleeding without causing tissue damage. Their efficacy has been excellent in non- variceal bleeding. The available clips differ in several features (open and close, clip rotation, disposable or not) with a common minimum channel size (2.8 mm). Their jaw length varies from 9 to 11 mm, making them ideal for lesions between 10 and 15 mm wide. Indications for positioning clips are: bleeding vessel in ulcer base, intractable bleeding after mucosal biopsy or bleeding at the site of polypectomy. If the ulcer base is fibrotic, tissue apposition with clips can be much more difficult. Typically, more than one clip is applied to the bleeding site.

A particular type of clips is represented by the over the scope clips (OTSC) system, (Ovesco, Tübingen, Germany). This device is composed of an application cap, which is mounted onto the distal tip of the endoscope and a connected releasing mechanism, installed on the handle of the scope. Unlike common endoscopic clips, the OTSC is able to compress larger quantities of tissue. The efficacy of this system has been proved for the same indications as standard hemoclips, even though at present its availability is still lower than common clips (26). Band ligation is mostly used in the treatment of esophageal varices, but its use has also been described in the management of Dieulafoy lesions, blue rubber bleb nevus syndrome, Mallory-Weiss, gastric ectasia, duodenal ulcers and treatment of haemorrhoids. In the colon caution must be taken when suctioning the lesion into the friction fit adapter to prevent full thickness entrapment, subsequent necrosis and perforation (5). Hemospray (TC-325) (Cook Medical, USA), a novel proprietary inorganic powder which achieves hemostasis by adhering to the bleeding site, provoking a mechanical tamponade and, by concentrating and activating platelets and coagulation factors, promotes thrombus formation. Hemospray can quickly cover large areas and does not require frontal view or direct contact with the bleeding lesion, although its application alone has not been proven to sufficient to manage profuse hemorrhages. The high rates of both acute hemostasis and recurrent bleeding suggest that Hemospray is probably best used as a temporary bridge toward more definitive therapy (27). Cautery therapy is based on the application of thermal energy to achieve coagulation of the tissue. It acts by denaturing or coagulating proteins and then through the evaporation of tissue water causing atrophy (28). Argon plasma coagulation (APC) is preferred for the treatment of angiodysplastic lesions as artero-venous malformations, bleeding ulcer and ablation of adenomatous tissue. It needs a non-contact device that uses argon gas. Coagulation is a few millimetres deep and a larger area of tissue can be treated at one time compared to bipolar electrocautery (1). Noncontact and contact coagulation have comparable efficacy for hemostasis, rebleeding, transfusion requirement and need for surgery, moreover are superior to pharmacotherapy alone; a systematic review performed on 49 adults showed that coagulation was superior to injection therapy or pharmacotherapy alone (28).

Surgery

In case GIB cannot clearly be identified and conservative therapies, either endoscopic or therapeutic imaging, have failed, surgery should be considered. Whenever possible, intraoperative endoscopy should be carried out to help clarify and localize the bleeding source. Directed segmental resection is the treatment of choice because of its low morbidity, mortality (about 4%) and rebleeding rate (about 6%) (7, 29).

Conclusions

Gastrointestinal bleeding may be a life-threatening condition. A well structures emergency treatment and timely diagnostic approach based on suspected cause of bleeding can significantly reduce mortality rates in these patients. Endoscopy plays a major role both in diagnosis and management of bleeding throughout the entire gastrointestinal tract. Nevertheless, cooperation with radiologists and surgeons is essential to cope with challenging clinical cases with the aim of a general optimization of acute gastrointestinal bleeding.

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