Uncontrolled bleeding of the gastrointestinal tract

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Purpose of review
Acute gastrointestinal bleeding is a frequent emergency situation, whose incidence will likely rise as a result of the increasing use of direct anticoagulants and of the medical progresses resulting in longer life expectancy with underlying comorbidities. Updated guidelines and improvements in the diagnostic and therapeutic tools are now available and will likely improve the management of massive gastrointestinal bleeding in the near future.

Recent findings
The assessment of severity has been improved by validated scores useable upon admission. Massive blood transfusion protocols and specific care in case of bleeding of patients treated with direct anticoagulants, including concentrates of coagulation factors and monoclonal antibodies are now available. The endoscopic management has been facilitated by the use of hemostatic powders and by the use of self-expanding metal stents in case of variceal hemorrhage. New diagnostic tools include emergency video-capsule endoscopy, multiphasic computed tomography angiography and enterography.

Summary
The implementation of multidisciplinary diagnostic and therapeutic algorithms for the management of massive bleeding requires a close collaboration between emergency physicians, intensivists, endoscopists, radiologists and surgeons. A sequential strategy involving each of these specialists is desirable for a successful management of acute and massive gastrointestinal bleeding.

Keywords
endoscopy, hemorrhage, hemorrhagic shock, interventional radiology, massive blood transfusion

INTRODUCTION

Acute gastrointestinal bleeding (AGIB) is a growing clinical concern. Schematically, there are three major sources of AGIB:

(1) Upper gastrointestinal bleeding (UGIB), which accounts for more than two-thirds of the AGIBs. UGIBs are subdivided according to the presence or absence of portal hypertension.
(2) Lower gastrointestinal bleeding (LGIB), which accounts for approximately 20% of all cases of AGIB [1▪▪].
(3) Small bowel bleeding (SBB, or obscure gastrointestinal bleeding, which accounts for approximately 5–10% of AGIB [2▪].

The present review is focused on massive gastrointestinal bleeding (MGIB), defined as the presence of AGIB and either a need for more than 10 units of packed red blood cells (PRBC) or the total replacement of blood volume in 24 h or a replacement of 50% of the blood volume in 3 h or blood loss of more than 1500 ml in 10 min [1▪▪,3,4▪▪].

This review aims to provide an update on the various aspects of the management of MGIB, supported by updated guidelines for the management of AGIB [1▪▪,5▪▪] and massive transfusion protocols. As the management of MGIB requires a multidisciplinary approach, the combination of the different diagnostic and therapeutic strategies (endoscopy, radiology, surgery, pharmacological treatments) must be carefully thought and planned. The referral to a tertiary center must be included in specific situations, whenever the local resources do not allow a proper management.

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KEY POINTS

- The management of massive gastrointestinal bleeding needs a multidisciplinary collaboration, including massive transfusion protocols, very early endoscopy and transcatheter arterial embolization.
- Bleeding patients treated with direct anticoagulants require a specific management.
- Hemostatic powders, self-expanding metal stents and emergency video-capsule endoscopy represent major improvements in endoscopic techniques.

EPIDEMIOLOGY

Even though the incidence of AGIB ranges approximately from 40 to 150 cases per 100 000 adults [5▪▪], the precise incidence of MGIB and its related mortality have not been recently reported. However, the likelihood of MGIB is probably rising as a consequence of medical progresses resulting in longer life expectancy with underlying comorbidities, and of the growing use of direct oral anticoagulants (DOACs) in contemporary medical practice [6,7].

DIAGNOSIS AND EVALUATION

The clinical diagnosis is usually easy, especially in case of UGIB, which is typically associated with hematemesis and melena or melena. However, more challenging presentations such as hematochezia can sometimes be reported in cases of LGIB, SBB or occasionally UGIB.

The evaluation of the severity of an AGIB can be performed using composite scores calculated from 'preendoscopic' variables available in the emergency department. Recent data collected, compared the ability of these scores to predict mortality. The highest predictive values were reported for the Glasgow–Blatchford, Rockall and AIMS65 scores [8▪▪,9]. Accordingly, the European guidelines recommend the use of the Glasgow–Blatchford score for preendoscopy risk stratification [5▪▪].

GENERAL MANAGEMENT

Most guidelines developed for the management of posttrauma hemorrhagic shock and massive transfusion protocols can be applied for the management of MGIB (Fig. 1). Basically, standard resuscitation maneuver is the first priority, with particular attention to the restoration of a correct circulating volume including airway protection especially in the presence of UGIB [10▪▪]. A rapid sequence induction of anesthesia is, therefore, recommended [11]. Blood products must be readily available. In most conditions a 1 : 1 PRBC : fresh frozen plasma (FFP) ratio is required to stabilize hemorrhagic shock [12▪▪]. As compared with higher thresholds, a PRBC transfusion threshold of 7 g/dl has been associated with less transfusion requirements, fewer side effects, less bleeding recurrence and an increased chance of survival at 6 weeks in two large randomized, controlled studies [13,14▪]. Hence, the 7 g/dl transfusion threshold ('restrictive' strategy) is recommended in most patients. Excessive transfusions can induce fluid overload and an increase in portal pressure and rebleeding. In case of particular risk of anemia (acute coronary syndrome, peripheral or cerebrovascular disease), a transfusion threshold of 9 g/dl is usually recommended [10▪▪,14▪]. Additional modalities include antifibrinolytic therapy

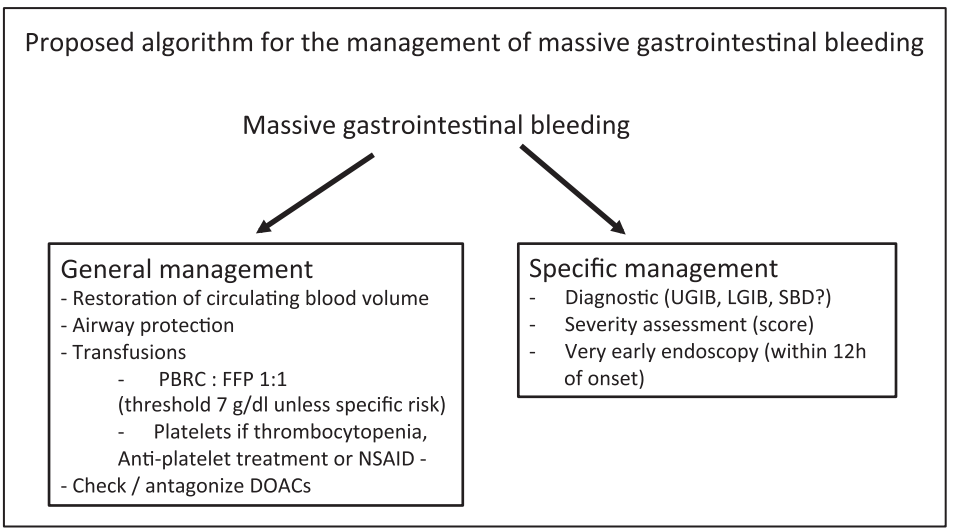

FIGURE 1. Schematic representation of the main steps of the general and specific management of massive gastrointestinal bleeding.

and fibrinogen transfusions as optional rescue therapies, but have not been validated in MGIB. The currently running HALT-IT (Haemorrhage ALleviation with Tranexamic acid – IntesTinal system) trial aims to assess the effects of traxenamic acid on AGIB-related mortality [15].

Whenever the patient is treated with anticoagulant or antiplatelet medications, specific measures must be applied at the time of initial resuscitation. Platelet transfusion is justified in cases of thrombocytopenia ($\leq$50 000/mm^3), use of nonsteroidal anti-inflammatory agents or antiplatelet agents [16]. A recent retrospective study reports a suggested four-fold increased risk of AGIB in patients treated with warfarin than with DOACs [17]. The DOACs are extensively used since a few years and include direct thrombin inhibitors (dabigatran) and inhibitors of factor Xa (rivaroxaban, apixaban). A causative role of dabigatran is confirmed by an abnormal thrombin clotting time. In such case, a rapid reversal of the effect of dabigatran can be achieved with idarucizumab, a monoclonal antibody fragment, recently authorized for marketing in Europe and USA [18]. A role of rivaroxaban or apixaban can be assessed by the plasma anti-Xa assay [6]. Inhibitors of rivaroxaban and apixaban (andexanet alpha and ciraparantag) are currently under development but not yet available for clinical use [7].

The DOACs are also cleared efficiently by hemodialysis, which may be a valuable alternative [19]. Finally, the effects of DOAC can also be inhibited with concentrates of purified factors II, VII, IX and X.

After hemodynamic stabilization and initiation of correction of coagulation disorders, specific treatment of bleeding must be initiated as quickly as possible. In most cases, very early endoscopy (less than 12 h after the onset of AGIB) is the first-line treatment [5▪▪], together with the pharmacological approach. In case of failure of standard endoscopic procedures to stop bleeding, novel endoscopic and radiological strategies have been recently validated.

ENDOSCOPY

Table 1 summarizes the different diagnostic and therapeutic endoscopic modalities, according to the site and source of bleeding. Standard hemostatic techniques used during endoscopic procedures include the injection of physiological saline, diluted epinephrine solution, macrogollaurylether (e.g. aethoxysclerol) or

Table 1. Tools for diagnosis and/or treatment

Endoscopy
UGIB: gastroscopy (utility erythromycin bolus before) diagnostic and therapeutic
Nonvariceal hemorrhage
Local injection
Thermic coagulation (high frequency coagulation, argon beam, thermal probe, microwave, etc.)
Mechanical hemostasis: hemostatic clip, over-the-scope-clip (OTSC)*
Hemostatic powder
Variceal hemorrhage (esophageal, gastric)
Variceal banding ligature (VBL)
Tissue adhesive glue: histoacryl (*N*-butyl-cyanoacrylate) for gastric varices, also associate with VBL
Injection of thrombin for gastric varices
Balloon tamponade (temporary): Sengtaken–Blakemore or Linton–Nachlas tube
Esophageal stenting
Hemostatic powder
Self-expanding metal stents
LGIB: colonoscopy (need bowel preparation): diagnostic and therapeutic
Local drug injection (diluted epinephrin)
Contact thermal coagulation (bipolar electocoagulation, argon plasma coagulation, heather probe)
Mechanical hemostasis: hemostatic clip, band ligation
SBB
Video-capsule endoscopy (VCE) (no preparation): diagnostic
Push enteroscopy: diagnostic and therapeutic
Deep enteroscopy: diagnostic and therapeutic

LGIB, lower gastrointestinal bleeding; SBB, small bowel bleeding; UGIB, upper gastrointestinal bleeding.

the application of clips, or thermic coagulation. In case of MGIB, recent technological developments have been validated and could represent salvage life-saving therapies, and/or first-line treatment in the near future. These advances include hemostatic powders, self-expanding metal stents (SEMS) and emergency video-capsule endoscopy (VCE).

Hemostatic powders are used to achieve hemostasis rapidly and efficiently, as a cohesive and adhesive clot is formed in contact with moisture. These sprayable powders are used for induction of immediate bleeding stop via the endoscope, and are neither absorbed nor metabolized within the mucosa, hence minimizing the risk of systemic toxicity [20▪]. Clinical practice with the available hemostatic powders confirmed the immediate stop of active bleeding, even in case of malignancies [21]. In a recent systematic review, Chen and Coll [22] proposed an algorithm where hemostatic powders should be used in bleeding lesions difficult to reach, or as rescue therapy in case MGIB, while awaiting a definitive therapy or the referral to a tertiary center.

In patients with a high risk of variceal rebleeding and advanced liver disease, SEMS appears as a promising option. The results of six recent case series ($n = 83$ patients) [23] and of a randomized controlled trial ($n = 28$) [24▪] confirmed the superiority of SEMS over balloon tamponade. Indeed, SEMS provided an effective hemostasis, a lower rate of complications and a better performance than balloon tamponade. A recent meta-analysis [25▪▪] ($n = 155$) concluded that SEMS were associated with less severe side effects than balloon tamponade, allowed a better control of bleeding, and could stay much longer than balloon tamponade (24 h for balloon tamponade, up to 14 days for SEMS). Hence, SEMS must be considered relatively early in rebleeding patients after a first-line pharmacological and endoscopic treatment. SEMS could also be considered as a bridge therapy to Transjugular Intrahepatic Porto systemic Shunt (TIPS), or surgical portal shunt, liver transplantation or relocation in a safer hemodynamic condition, or even as a definitive treatment [6].

The diagnosis of SBB is usually challenging and require push enteroscopy (upper endoscopy with long pediatric colonoscope, or 250 cm length endoscope, until 45–60 cm up to 90 cm beyond the ligament of Treitz) or deep enteroscopy (oral approach: 240–360 cm from pylorus, or rectal approach: 102–140 cm from ileocacal valve).

Emergency VCE can be successfully used in case of severe SBB, or obscure-overt gastrointestinal bleeding, whenever the oesogastroduodenoscopy and the colonic endoscopy did not identify the source of bleeding [26]. The combination of VCE with emergency balloon enteroscopy to stop bleeding have been recently suggested [27▪].

Table 2. Recent nonendoscopic options

Radiology
Computer tomographic angiography (CTA): diagnostic
Computer tomographic enteroscopy (CTE): diagnostic
Magnetic resonance enterography: diagnostic
Digital subtraction angiography
Surgery
Total/subtotal/gastrectomy
Total or limited colectomy: according to the site of bleeding suspected
Portal shunt for portal hypertension

RADIOLOGY

Recent progresses in the radiological techniques include improvements in the diagnostic techniques, and in therapeutic approaches via endovascular interventions.

Whenever the source of bleeding has not been identified, or in case of failure of the medical and endoscopic treatment, diagnostic imaging is required (Table 2). Computed tomography angiography (CTA), computed tomography or magnetic resonance enterography are noninvasive radiologic imaging [28]. CTA allows the detection of bleeding rates as low as 0.3 ml/min, with higher specificity (92–95%) than sensitivity (50–86%) [29]. Multiphasic CT offer a higher sensitivity compared with unique arterial acquisition [30]. In case of MGIB, the likelihood of high bleeding rate is higher, implying a higher sensitivity of CTA than in low-rate bleedings [31]. However, if the bleeding is not acute or continuous, the sensitivity of CTA decreases to approximately 40% [32]. In case of LGIB, CTA is efficient and could localize the bleeding source in most cases [33].

CTE requires the administration of large volumes of neutral oral contrast, which can mask bleeding by dilution. Moreover, high volumes are not easy to administer in a patient with massive bleeding. Multiphasic CTE should be reserved for occult GIB and/or slow bleeding [34].

Whenever emergency endoscopy is unavailable, unable to control or localize the source of UGIB, visceral arteriography should be considered [35]. Transcatheter arterial embolization (TAE) has a high technical success rate (69–100%) and is associated with lower complication rates than transcatheter vasopressin infusion [36,37]. Angiography can identify a bleeding source in up to 80% of cases, with a

primary success rate for TAE of 80% [38]. Such a high success rate of TAE has resulted in a diminishing need for surgical intervention, which may be used in event of rebleeding [38].

In LGIB, TAE should be considered whenever conservative treatment has failed and CTA localized the bleeding site. TAE has a high rate (96%) of immediate hemostasis [39].

TIPS or even direct intrahepatic portocaval shunt (DIPS) are considered in case of acute variceal bleeding [40], which persists despite medical and endoscopic treatment. The use of TIPS in the setting of acute variceal hemorrhage is limited but a recent study suggests that if early risk stratification can be performed, early TIPS insertion could improve overall outcomes [41]. DIPS appears to be a well tolerated, expedient and effective treatment for patients with acute variceal haemorrhage, who are poor anatomic candidates for TIPS creation or who have undergone unsuccessful TIPS attempts [42].

SURGERY

A surgical consultation should be requested in patients with high-risk clinical features and ongoing bleeding. In general, surgery for acute LGIB should be considered after failures of the endoscopic or radiological treatments (Table 2). The decision of surgery should take into consideration the extent and success of prior bleeding control measures, the severity and source of bleeding, and the level and severity of comorbidities. In case of surgery, the source of bleeding should be localized whenever to minimize the risk of continued or recurrent bleeding from an unresected culprit lesion [1▪▪]. A recent retrospective study suggests that surgery should be considered early in case of massive or recurrent right diverticular hemorrhage [43].

PHARMACOLOGY

Proton pump inhibitors

Proton pump inhibitors (PPI) remain the first treatment of choice for suppressing gastric acid and preventing rebleeding for acute peptic ulcers with UGIB, but controversy still exists about the correct dosage to apply (Table 3).

A recent review [44] concludes that PPI may be given with equal efficiency as an intravenous bolus injection (80 mg i.v. bolus, followed by 8 mg/h infusion rate for 72 h), or as an intermittent intravenous or oral dosing (40 mg/12 h).

PPIs before endoscopy aims to improve the formation of the platelet nail by maintaining the gastric pH above 6. However, in a large meta-analysis of six randomized and controlled trials, there was no reported benefit of PPI just before endoscopy over initiation after endoscopy [45].

Table 3. Recommended pharmacological interventions in current situations

UGIB
Proton pump inhibitor
Splanchnic vasoconstrictors: somatostatin–octreotide or glypressin–terlipressin
Variceal bleeding:
Proton pump inhibitor
Splanchnic vasoconstrictors: somatostatin–octreotide or glypressin–terlipressin
Antibiotics
Emergency endoscopy
Erythromycin

UGIB, upper gastrointestinal bleeding.

Splanchnic vasoconstrictors (somatostatin–octreotide or terlipressin–vasopressin)

Somatostatin and its long-acting analogue octreotide, inhibits the release of vasodilating hormones such as glucagon, indirectly causing splanchnic vasoconstriction and a decrease in portal blood flow. These drugs are usually used for the management of variceal bleeding, or as adjuvant therapy in case of bleeding ulcer disease. In this latter situation, the beneficial effects are related to the decrease of splanchnic blood flow, the inhibition of gastric acid secretion. In case of variceal bleeding, recent guidelines [46▪▪] strongly recommend the initiation of somatostatin, octreotide or terlipressin before any endoscopic intervention to reduce the risk of rebleeding and to lower mortality, and the continuation of treatment until hemostasis is achieved or for up to 5 days. In a recent prospective, multicenter, randomized study performed on 780 patients, the efficiency of vasopressin or its analog terlipressin was found similar to somatostatin and octreotide [47].

Antibiotics

Prophylactic antibiotics are usually proposed to cirrhotic patients with acute variceal bleeding, because of their vulnerability to infection, in general aerobic Gram-negative bacilli. Recent guidelines [46▪▪] recommend the use of antibiotics that provide Gram-negative cover, as mortality, bacterial infections and the rate of early rebleeding were all reduced in treated patients. In 2016, Agarwal *et al.* [48] reported

a trend towards lower rate of early and late rebleeding, infection rate and mortality in a prospective randomized trial of 60 patients randomized to prophylactic ofloxacin.

Erythromycin

Erythromycin is a macrolid antibiotic, which also binds to motilin receptors, thereby inducing gastric emptying. Its use before an urgent endoscopy, allows a better visualization of the stomach, and thus reduce the need for second look endoscopy, and length of hospital stay. [49▪,50]. Hence, erythromycin is recommended before urgent gastroscopy for UGIB [5▪▪].

CONCLUSION

MGIB is a frequent emergency and life-threatening situation. The availability of blood products, including purified coagulation factors and DOACs antagonists, emergency endoscopy and angiography are required. Emergency interventions such as hemostatic powders and splanchnic vasoconstrictors can help to stabilize a bleeding patient before a transfer to a referral center. In any case, a multidisciplinary sequential strategy guided by diagnostic and therapeutic algorithms is needed for the management of massive bleeding and requires a close collaboration between emergency physicians, intensivists, endoscopists, radiologists and surgeons.

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Conflicts of interest

There are no conflicts of interest.

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