

## Massive Gastrointestinal Bleeding in the Emergency Department

**María Camila Arango-Granados\* and Virginia Zarama**

*Emergency Department, Fundación Valle del Lili, ICESI University, Colombia*

**\*Corresponding Author:** María Camila Arango-Granados, Emergency Department, Fundación Valle del Lili, ICESI University, Colombia.

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### Abstract

Gastrointestinal bleeding is one of the most common gastrointestinal emergencies. In most cases, bleeding is controlled by standard therapeutic strategies relative to each particular pathology. However, sometimes bleeding is massive and refractory to conventional strategies. The current review aims to address the available evidence regarding the advanced therapeutic interventions for massive GIB refractory to conventional therapies. For this purpose, we performed a sensitive search strategy in SciELO, MEDLINE and Cochrane databases using terms related to gastrointestinal bleeding, massive gastrointestinal bleeding, high-variceal and non-variceal gastrointestinal bleeding, low digestive bleeding, non-traumatic hemorrhagic shock and Resuscitation Endovascular Balloon Occlusion of the Aorta (REBOA). Literature supports that the timely diagnosis and immediate start of resuscitation with blood products is essential. Additionally, the opportune consideration of angioembolization, surgery or REBOA could result in a reduction in the morbidity and mortality associated with this catastrophic condition. Therefore, the coordinated and collaborative management of all the specialists involved is of paramount importance.

**Keywords:** *Gastrointestinal Hemorrhage; Hemorrhagic Shock; Digestive System Endoscopy; Angiography; Therapeutic Embolization; Balloon Occlusion*

### Abbreviations

GIB: Gastrointestinal Bleeding; RBC: Red Blood Cells; REBOA: Resuscitation Endovascular Occlusion of the Aorta

### Introduction

Gastrointestinal bleeding (GIB) is one of the most common gastrointestinal emergencies. Its incidence in adults is estimated at 40 - 150/100,000 inhabitants-year. There are three sources of GIB: upper, occult and lower. The first, which includes all bleeds whose origin is proximal to the ligament of Treitz, represents 70% of all the cases. Low GIB refers to pathologies of the colon and represents 20% of cases. Finally, small bowel bleeding, also called "occult" GIB, is the least frequent (5 - 10% of cases) [1].

The most common pathologies related to GIB [2-4] are shown in table 1.

In most cases, bleeding is controlled by standard therapeutic strategies relative to each particular pathology. However, sometimes bleeding is massive and refractory to conventional strategies and requires advanced therapeutic interventions. Classically, the literature defines massive GIB as one that requires transfusion of > 10 units of red blood cells (RBC), the replacement of all the blood volume in 24h, the replacement of 50% of the blood volume in 3h, or the one that generates estimated losses > 1.5 liters [5,6]. Still, we believe that massive GIB should also be defined according to the patient's individual hemodynamic response to blood loss. In accordance, persistent hemodynamic instability despite aggressive volume and/or hemostatic resuscitation (without quantity restriction) is also considered as massive GIB.

Upper GIB	%	Occult GIB	%	Lower GIB	%
Ulceropeptic disease	20 - 67	Angiodysplasia	35	Diverticulosis	30 - 65
Erosive disease	4 - 31	Ulcers	13	Ischemic colitis	5 - 20
Variceal	4 - 20	Tumors	9	Hemorrhoids	5 - 20
Esophagitis	3 - 12	Varices	3	Colorectal polyps/tumors	2 - 15
Mallory-Weiss	4 - 12			Angioectasy	5 - 10
Malignancy	2 - 8			Post polipectomy	2 - 7
Esophageal ulcers	2 - 6			Inflammatory Intestinal Syndrome	3 - 5
Idiopathic/Unknown	3 - 19			Infectious colitis	2 - 5

**Table 1:** Causes of Gastrointestinal Bleeding and their frequencies according to location.

## Aims and Methods

This is a non-systematic review that aims to address the available evidence regarding the advanced therapeutic interventions for massive GIB refractory to conventional therapies. For this purpose, we performed a sensitive search strategy in SciELO, MEDLINE and Cochrane databases, using terms related to gastrointestinal bleeding, massive gastrointestinal bleeding, high-variceal and non-variceal gastrointestinal bleeding, low digestive bleeding, non-traumatic hemorrhagic shock and Resuscitation Endovascular Balloon Occlusion of the Aorta (REBOA). All studies written in English or Spanish, performed in adult humans (aged 18 years or older), were revised. As massive GIB is the focus of this review, articles about initial management of GIB in non-life-threatening situations were excluded.

## Results and Discussion

### Diagnosis and Initial Resuscitation

In massive GIB, early recognition of hemorrhagic shock and immediate therapeutic actions to stop the bleeding are of paramount importance, since the approximate time from the onset of massive bleeding to death is about 2 hours [7]. The signs and symptoms of hemorrhagic shock, especially from hidden sources of bleeding, are often subtle. In most patients, robust compensatory mechanisms make hypotension an insensitive indicator of shock until more than 30% of the blood volume has been lost. The subtlest clinical signs suggestive of shock include anxiety, tachypnea, weak peripheral pulse and cold extremities with pale or mottled skin [8].

Laboratory tests to evaluate tissue hypoperfusion include base excess and lactate obtained from blood gas analysis. Other useful laboratory values in a patient with severe hemorrhage include hemoglobin and INR, which can be used to predict the need for a massive transfusion [9]. The platelet count and fibrinogen levels should be measured and normalized. Electrolytes, including potassium and calcium, should be measured early and often during resuscitation with blood products, as they can fluctuate significantly [10,11].

Massive transfusion protocols provide blood components to the patient's bedside in standardized proportions. These protocols provide a survival benefit for patients with acute hemorrhage [12]; any delay in the activation of the protocol is associated with an increase in mortality [13].

The proportion of red blood cells, plasma and platelets that is clinically beneficial has not been conclusively defined. However, two prospective studies [14,15] and a systematic review [12] indicate that a ratio of plasma: platelets: red blood cells close to 1:1:1 is safe and reduces short-term mortality due to traumatic hemorrhage. In case of patients with non-traumatic hemorrhage, a recent retrospective study showed that a ratio of platelets to red blood cells of 1:2 reduced mortality in the first 48 hours [6].

Blood products contain citrate, which is rapidly metabolized by the liver in healthy people. However, in patients with hemorrhagic shock who are receiving a large volume of blood products, citrate can become toxic, with potentially fatal hypocalcemia and progressive coagulopathy [16,17]. Therefore, the empirical administration of calcium during high-volume transfusions (e.g. after the transfusion of the first 4 units of any blood product) should be combined with frequent measurements of electrolyte levels.

There are controversies about the utility of tranexamic acid in massive GIB. A recent meta-analysis concluded that tranexamic acid may have a beneficial effect on mortality, but the quality of individual studies is not sufficient to ensure these results. In addition, tranexamic acid did not reduce mortality in patients in whom bleeding control was achieved with early endoscopic therapy. Additional controlled clinical trials are needed to clarify whether tranexamic acid has a beneficial effect on severe or uncontrolled GIB [18]. To date, tranexamic acid seems reasonable, especially in patients who for some reason cannot receive an early endoscopic management.

Some patients will require additional vasopressor support to optimize mean arterial pressure and cerebral perfusion pressure while controlling the source of bleeding [19]. The most studied drugs for this purpose are noradrenaline [20-22] and vasopressin [23]. There should be no hesitance initiating vasopressor support when felt necessary.

Finally, according to the American College of Cardiology Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants, the immediate reversal of anticoagulation is recommended in cases of massive, life-threatening GIB. For further specification of the reversion techniques, the reader is referred to the original document of the aforementioned Consensus [24].

Diagnosis and Initial Resuscitation Key Messages
<ul style="list-style-type: none"> <li>• It is recommended to activate the massive transfusion protocol in cases of massive gastrointestinal bleeding with hemodynamic instability on admission.</li> <li>• The administration of IV Calcium is recommended in concomitance with the administration of &gt; 4U of blood products, or from the beginning in cases of hypocalcemia.</li> <li>• It is recommended to start vasopressor therapy with noradrenaline or vasopressin in cases of severe hypotension refractory to resuscitation with intravascular volume.</li> <li>• The administration of 1g of tranexamic acid is recommended for patients who cannot receive early endoscopic treatment.</li> <li>• Immediate reversal of oral anticoagulants is recommended in cases of massive life-threatening bleeding.</li> </ul>

**Bleeding control therapies**

**Variceal bleeding**

One successful endoscopic treatment for the management of variceal bleeding is band ligation [25]. This strategy is successful in 88-90% of the cases, is superior to sclerotherapy in rebleeding rates (31 vs 47% respectively, OR 0.52, 95% CI 0.37 - 0.74) and does not increase portal pressure [26]. Other emerging endoscopic tools, such as the endoscopic ultrasound- guided insertion of coils and cyanoacrylate, are also proposed [27], however limited data exists on such therapies in patients with active bleeding and hemorrhagic shock.

In cases of failure to the initial endoscopic approach to control bleeding, balloon tamponade and self-expanding metal stents are proposed. A recent controlled clinical trial compared these two strategies in 28 cirrhotic patients with upper variceal GIB refractory to medical and endoscopic management, for the primary composed outcome of bleeding control and absence of serious complications at day 15. The majority were Child-Pugh class B/C, with MELD scores ranging from 9 - 32. Both cohorts had hematocrits on admission ranging from 11 - 44, the number of PRBC transfused before inclusion ranged from 0 - 20 and 46 - 66% were in shock at index bleed, with no differences between subgroups. The group randomized to self-expanding stents reached the primary outcome in 66% of the cases, versus 20% in the group randomized to balloon tamponade. In the latter, there were more deaths associated with bleeding and one case of esophageal rupture (vs none in the group with stents). In addition, self-expandable stents were maintained for up to 12 days, versus 2 days maximum for balloon tamponade [28].

A meta-analysis on the use of self-expanding stents found a bleeding control rate close to 96% [29]. The rate of adverse events directly related to the device (esophageal rupture, esophageal ulcers, bronchoaspiration, device migration) reached 8%, although it was significantly lower than the rate of adverse events related to the balloon (40%) [28].

Finally, most studies on self-expanding stents use this strategy as a bridge to a definitive intervention such as Transjugular Intrahepatic Portosystemic Shunt (TIPS) or transplantation, and some as a bridge to conservative management [29].

In selected cases, more advanced therapies such as emergency TIPS or Emergency Surgical Portocaval Shunt (ESPS) are advised. Orloff, *et al.* published a controlled clinical trial comparing these two strategies in 154 cirrhotic patients with high variceal GIB. To highlight, narcotic addiction and type 2 diabetes were the more common comorbidities (19.7 - 24.4% and 11.8 - 14.1%, respectively); < 4% had concomitant hypertension, pulmonary, coronary or renal disease. Around 50% were actively bleeding on admission, and Hb levels were as low as 2.3 mg/dL in some patients. The study achieved a follow-up of 100% at 24h and 85% at 5 - 10 years. Immediate bleeding control rate was achieved in 80% of patients treated with TIPS, but only 22% of these patients reached bleeding control in the long term. On the contrary, ESPS was associated with an immediate bleeding control rate of 100%, and a long-term bleeding control of 97%. Survival was greater in the group randomized to ESPS vs the group randomized to TIPS (10 years vs. 1.99 years,  $p < 0.001$ ). At 21 days, stenosis or occlusion of TIPS occurred in 84%, 63% were reviewed and the revision failed in 80% of the cases. However, encephalopathy was 3 times higher in patients randomized to ESPS compared to patients randomized to TIPS [30].

A post hoc analysis of a randomized clinical trial of emergency sclerotherapy vs ESPS found that, from the entire cohort (211 patients), 13 were referred for transplantation and 4 were finally transplanted (with an average time on waiting list of 3 weeks). All the transplanted patients died after surgery. Finally, none of them had been randomized to an ESPS [31]. This, added to the greater technical difficulty of performing a liver transplant in patients with a portocaval shunt, suggests that this emergency strategy should be reserved for patients with contraindications for transplantation. However, evidence is still scarce.

Variceal Bleeding Key Messages
<ul style="list-style-type: none"> <li>• Band ligation is recommended as a first line strategy for the endoscopic control of variceal bleeding.</li> <li>• In cases of failure or impossibility of performing a band ligation, self-expandable stents are recommended as a rescue strategy.</li> <li>• In cases of failure to band ligation and self-expandable stents, emergency TIPS or ESPS could be considered.</li> <li>• ESPS seems to be more appropriate for patients with contraindications for liver transplantation.</li> </ul>

## Upper non-variceal GIB

### Endoscopic management

Patients with massive, non-variceal, upper GIB require an initial endoscopic approach aiming to control the source of bleeding. A recent cohort study conducted in the United Kingdom in patients with upper non-variceal GIB, found that in the subgroup of patients with hemodynamic instability, performing the endoscopy in the first 6 - 24h was associated with a lower risk of in-hospital mortality (OR 0.73, 95% CI 0.54 - 0.98). In the entire cohort, there were high-risk stigmata in 45% of the cases, and 2.7% were refractory to endoscopic management [32]. Early endoscopy has also demonstrated a substantial reduction in the length of hospital stay adjusted for risk and better control of bleeding in high-risk patients, which supports the routine use of early endoscopy unless there are specific contraindications [33]. However, a concrete definition of early endoscopy in cases of massive life-threatening GIB is not readily available.

### Angioembolization

Angioembolization for GIB refractory to endoscopic management has a technical success rate ranging from 89 - 100% and a clinical success rate between 44 - 94%. Studies report a visualization of active extravasation in approximately 54% of cases. Rebleeding rates with this therapy are reported between 9 - 66%; factors associated with greater rebleeding are coagulopathy at admission and the use of coils as the only embolic agent. Finally, the complications associated with the procedure occur in approximately 9% of cases [34].

It has been reported that the bleeding source is not visible in 33% of the angiograms [35]. In these cases, empirical angioembolization has been proposed as an alternative strategy. There is a prospective analysis of 59 patients with GIB due to duodenal ulcers who were taken to angioembolization, and in the absence of an identifiable lesion, empirical embolization of the large segments of the gastroduodenal artery and superior or posterior pancreaticoduodenal artery was performed. Significant comorbidities, such as prior coagulopathy (43 - 47%), heart disease (19 - 22%), diabetes (17%), lung disease (9 - 11%), chronic renal insufficiency (11 - 13%) and chronic liver disease (8 - 9%), were present in this cohort. In addition, 66% had massive bleeding on admission (> 4U RBC transfused, SBP < 90 mmHg, HR > 100). This study reported a technical success of 100%, a clinical success of 86% and recurrence of 14%. The rate of duodenal stenosis after empirical embolization was of 6%. None of these rates were statistically different to those from selective embolization [36].

Another retrospective cohort study of 115 patients (mainly oncologic) with upper non-variceal GIB who underwent angioembolization, analyzed 30-day clinical outcomes in the following groups:

- **Group 1:** No angiographic abnormality, no embolization.
- **Group 2:** No angiographic abnormality, empirical embolization.
- **Group 3:** Angiographic abnormality, embolization.

This study did not find significant differences between groups 1 and 2 in terms of primary hemostasis at 30 days, duration of hemostasis or survival. However, in the subgroup of patients with duodenal ulcers, there was a greater requirement for additional interventions in the group that did not receive embolization vs the group with empirical embolization ( $p = 0.03$ , RR 0.46, 95% CI 0.23 - 0.92, NNT 2) [37]. In this study there was no report on the complications associated with empirical embolization.

### Surgery

The last strategy for the control of massive bleeding refractory to the previous therapies is surgery. A retrospective cohort analysis of 90 patients with non-variceal GIB, with high transfusion requirements on admission (median units PRBC = 19), who underwent angioembolization or surgery due to endoscopic failure, did not find differences in 5-year survival between the two groups [38]. To highlight, patients had high risk comorbidities for surgery such as ischemic heart disease (47 - 58%), hypertension (27 - 35%) and COPD (10 - 12%),

with no difference between subgroups [38]. Similarly, another cohort study did not find statistically differences in 30-day mortality between the two groups (25% vs. 30.4%,  $p = 0.77$ ), but reported a higher rate of complications in the group undergoing surgery (67.9% vs 40.6%,  $p = 0.01$ ) [39]. However, rebleeding rates are lower in patients who undergo surgery, vs. those who undergo angioembolization (12.7% vs 46.7%,  $p < 0.005$ ) [40].

## REBOA

Endovascular occlusion of the aorta is a new strategy for the control of hemorrhagic shock. It is inserted percutaneously (with ultrasound-guided or open technique) in the common femoral artery and advanced until the descending thoracic aorta. A balloon is inflated in the aorta and bleeding control is achieved below the balloon level. Today, REBOA catheters that require as small as 7 Fr introducers are available [41]. Initially, REBOA was described for patients with shock of traumatic origin, however its use has already been expanded to non-traumatic massive bleeding [41]. From 1986 to 2015, there were 4 cases of massive GIB who underwent REBOA, 3 of which were receiving CPR simultaneously while the balloon was being inflated. An improvement in hemodynamics was achieved in the 4 cases, and 3 survived [42]. There are no reports of complications in this group. Subsequently, a published series of 8 cases of massive GIB treated with REBOA reported that 7 had a marked improvement in hemodynamic, 2 of them re-bleed and 6 survived. The total occlusion time ranged from 20 to 145 minutes [42].

A Japanese cohort study compared the clinical course of trauma versus non-trauma patients treated with REBOA. In the 36 patients with non-traumatic hemorrhage, 69% had bleeding of abdominal origin. The time to occlusion of the balloon was of 104 minutes, and the total duration of occlusion was of 18 - 68 minutes. A positive hemodynamic response was observed in 81% of the cases, mortality at 24h was of 19%, and in-hospital mortality was of 68% (the majority - 57% - due to multiple organ dysfunction, and 17% due to bleeding) [43].

Finally, a descriptive study of 11 patients with non-traumatic abdominal bleeding managed with REBOA, of whom 27% had GIB, reported a time to balloon occlusion of 62 - 209 minutes, hospital mortality of 36% and mortality due to non-controllable bleeding of 9%. There were no reported complications [44].

REBOA can be a valuable tool for the emergent control of massive GIB as a bridge to definitive therapy. The rapid improvement in hemodynamics is consistent in the literature. The next step is to demonstrate the potential clinical benefits of its use, and more robust clinical studies are needed to prove its efficacy.

## Low gastrointestinal bleeding and occult digestive bleeding

### Endoscopic management

For cases of low GIB, the ideal time for colonoscopy remains a matter of debate. There is a study in 121 patients with severe hematochezia due to diverticular disease that led patients to urgent colonoscopy (in the first 6 - 12). In case of recurrence of severe bleeding, the first 73 patients underwent hemicolectomy and the following 48 a new endoscopic treatment. In the latter subgroup, active bleeding was found in 50% of the cases, hemostasis was achieved in 100%, and none of the patients had an emergency hemicolectomy [45].

In addition, a randomized clinical trial allocated 100 patients with acute lower GIB to receive standard treatment (scintigraphy, angiography, embolization and elective colonoscopy) or early endoscopy (< 8h) with a rapid 4-6L PEG colon preparation [46]. 60 - 68% of these patients were in hemodynamic stability at admission, without differences between the study groups. Although the study did not find statistically significant differences between urgent colonoscopy and standard care for the primary endpoint of early or late re-bleed

### Upper GI Bleeding Key Messages

- Early endoscopic management is recommended for patients with upper non-variceal massive GIB, refractory to initial resuscitation.
- Angioembolization is recommended as a rescue strategy in upper non-variceal massive GIB, refractory to endoscopic management.
- Empirical angioembolization could be considered in upper non-variceal massive GIB, in the absence of identifiable lesion in the initial angiography, persistence of hemodynamic instability and very high surgical risk.
- Surgical resection of the potential source of upper non-variceal GIB is recommended as the ultimate rescue strategy in patients with massive GIB refractory to endoscopic management or angioembolization, or in cases where these procedures are not available or cannot be performed.
- Early insertion of a 7 Fr femoral introducer could be considered in patients with massive non-variceal GIB, refractory to resuscitation and initial endoscopic management if REBOA catheter and trained personnel are available for insertion.
- The use of a REBOA catheter could be considered in patients with massive non-variceal GIB, refractory to initial endoscopic management and with persistent severe hemodynamic collapse, as a bridge to definitive therapy.

(22% vs 30%), nor for the secondary endpoints of mortality (2% vs 4%) and hospital length of stay (5.8 vs 6.6 days), there was a general trend in favor of urgent colonoscopy. This study, although not powered, highlights the potential role of colonoscopy, particularly when performed early in the course of severe diverticular hemorrhage. Special attention must be taken in order to achieve a good colon preparation in a short period of time.

### Angioembolization

In cases of persistent massive low GIB, refractory to endoscopic management or whose source is not clearly identifiable by this means, angioembolization has been considered as a rescue strategy. Available data reveal that in patients with lower GIB (albeit mainly not massive), primary hemostasis is achieved in 96% of cases, 22% have early rebleeding, 22% have minor complications and 17% have major complications (those that require surgery or result in death) [47].

There is a retrospective analysis of 83 patients with GIB who underwent angiography, which included patients with occult and lower GIB (63% of all cases). In the entire cohort, 58% had cardiac disease and 54% were on anticoagulants. Transfusion requirements ranged from 0 - 9 units of PRBC, and 67% of those with active extravasation on angiography had SPB < 90 mmHg. 15 cases received embolization (8 of which corresponded to low GIB). In this subgroup 73% had hemodynamic instability, 53% re-bleed and 13% required subsequent surgical intervention. The 30-day mortality was of 33% and technical success was reached in 80% of the cases. Three patients with medium and low GIB, in whom no active extravasation was found, were taken to empirical embolization. One of them had a major complication (mesenteric ischemia) [48]. The invasive nature and potential risks of mesenteric angiography and embolization make it the second line of management after endoscopy in most cases.

A reasonable strategy to locate the source of bleeding prior to angioembolization is angiography by tomography. In patients with severe low GIB, this tool has a sensitivity of 88.6%, specificity of 100%, PPV of 100% and NPV of 90% for the diagnosis of active bleeding [49]. For this reason, in cases where the clinical status of the patient allows transportation to tomography suit, this diagnostic strategy should be considered to improve diagnostic performance of the conventional angiogram.

#### Low gastrointestinal bleeding and occult digestive bleeding Key Messages

- Early endoscopic management (6 - 12h) is recommended in patients with massive low GIB, refractory to initial resuscitation. A rapid 4 - 6L PEG colon preparation can be considered.
- In cases of persistent massive low GIB refractory to endoscopic management, or in whom the procedure is technically not possible, angioembolization could be considered as a rescue strategy.
- Empirical embolization is not recommended in cases of low GIB.
- If possible, angiography by tomography is recommended as an initial diagnostic strategy to improve the diagnostic performance of angiography .

## Conclusion

Massive gastrointestinal bleeding is a challenge for the emergency physician. The timely diagnosis and immediate start of resuscitation with blood products is essential. Additionally, it is necessary to bear in mind the therapeutic alternatives available for cases in which bleeding is refractory to conventional management.

The timely consideration of angioembolization, surgery or REBOA could result in a reduction in the morbidity and mortality associated with this catastrophic condition. Therefore, the coordinated and collaborative management of all the specialists involved is paramount.

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## Conflict of Interest

Authors declare no conflict of interests.

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