# GASTROINTESTINAL BLEEDING MANAGEMENT

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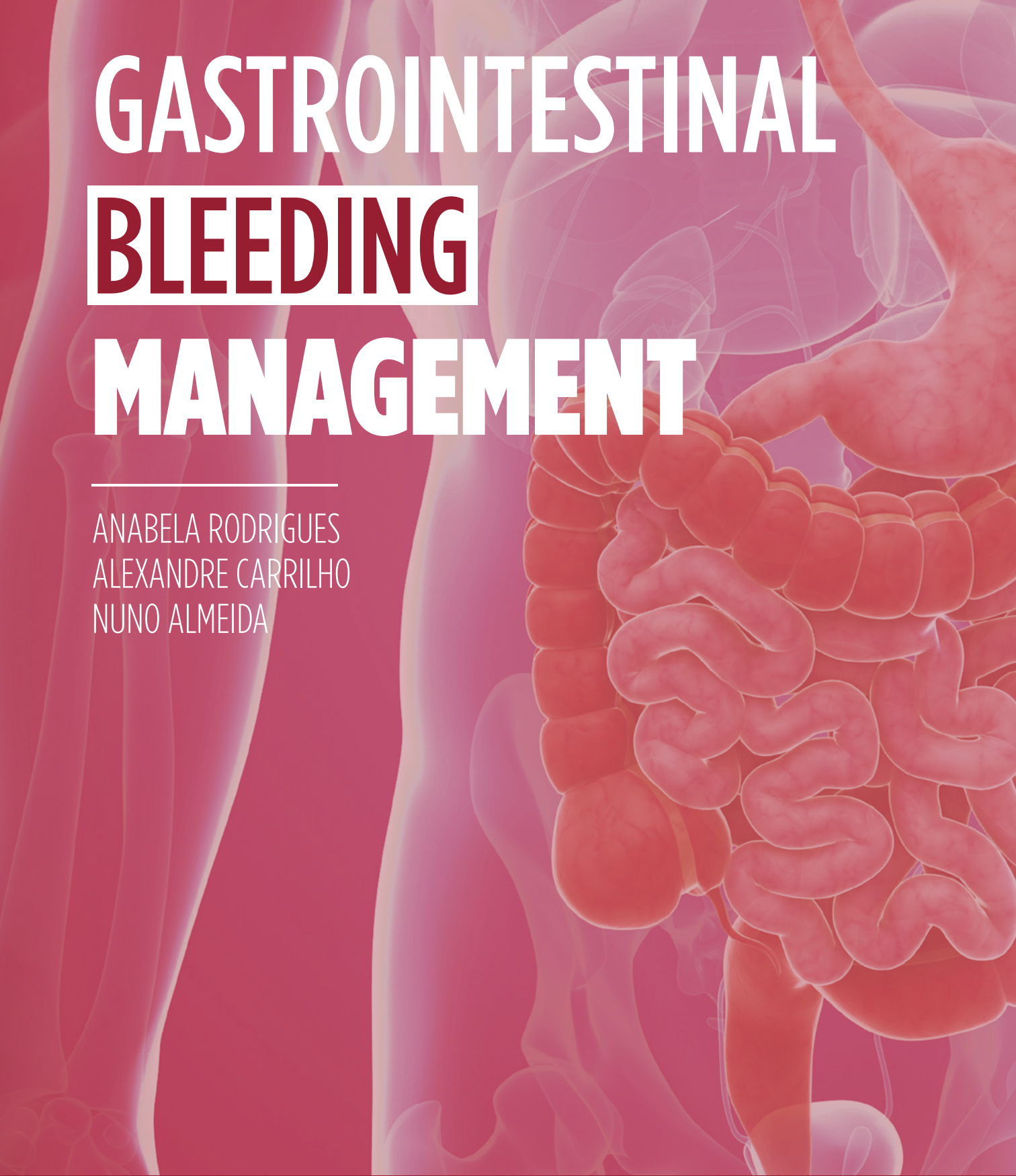

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Acknowledge to all authors, who are responsible for the scientific content for their own chapters.

# Preface

## Rui Tato Marinho

The present book results from a long, extensive, and multidisciplinary teamwork.

It has been a pleasure to be part of this team, exceptionally well-coordinated by Dr. Anabela Rodrigues.

The main topic of the book is Blood, that mythic, mystic, deeply red element. Red gold? Why not.

Blood and its derivatives arrive at the human veins after a long journey, also resulting from a coordinated teamwork with highly restrictive safety rules. It is a multi and interdisciplinary team, outlined in the "High-Performance Team" philosophy.[1,2]

Behind a single transfusion lies a group of several professionals – including physicians, nurses, and senior diagnostic and therapeutic technicians – from the Immune-hemotherapy, Anesthesiology, Gastroenterology, Emergency, and Surgery specialties.

Blood is unquestionably a precious good, and its arrival at someone's vein is the final path of a long humanitarian, technical, and technological journey.

In the setting of bleeding, there is a High-Performance Team on one side and a human being on the other, who is often in a situation of high fragility (frailty syndrome) and has a real risk of death that can go from 7% to 25%. This percentage varies according to age, comorbidities, multimorbidities, antiplatelet therapy, and anticoagulation.[1,2]

Interventional algorithms are a world, sometimes quite complex, as shown in this book. They are a world of scores and checklists to uphold a highly professional medical practice. In only a few pages in this book are depicted decades of investment, with a great spirit of public and humanitarian service from the very best Portuguese professionals.

By the end of this reading, I am sure we will be better professionals and more informed in the approach to our patients 24 hours a day, seven days a week.

It is a world of blood (our red gold), sweat (for the complexity of technological processing and performance of health professionals), and tears (for those who suffer and bleed to death). It is, in fact, Blood, Sweat, and Tears.*

*Blood, Sweat & Tears was a North American rock and roll band. It was created in 1967 in New York by Al Kooper, Jim Fielder, Fred Lipsiues, Randy Brecker, Jerry Weiss, Dick Halligan, Steve Katz, and Bobby Colomby. The band fused jazz with rock or pop into something hybrid that came to be known as “jazz-rock”.

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# Introduction

## Rosário Órfão

Gastrointestinal bleeding (GIB) is a frequent condition in the Emergency Department and management of these patients can be challenging. Although specific guidelines for GIB management have been published, many unanswered questions persist. Patients with GIB can be treated in big hospital centers, with availability or proper equipment and Transfusion Medicine, Gastroenterology, and Anesthesiology experts, or in small centers or primary clinics without adequate resources or experts.[1]

In 2011, the Share Network Group was created, with the support of CSL Behring. It included physicians from different specialties, but mainly Anesthesiology and Transfusion Medicine, with interest and experience in transfusion, management of patients with coagulopathy, and blood loss in different clinical settings. Important aspects of point-of-care monitoring and prevention and management of blood loss have been discussed with acknowledged experts, and the group has participated in Share Point Meetings, a moment of public discussion, every year.

The Share Network Group developed three intervention algorithms on acute coagulopathic bleeding in the perioperative, trauma, and obstetric settings, which were presented in several meetings, including the Annual NATA Symposium in 2014 and the meeting from *Sociedade Espanhola de Transfusão Sanguínea* (SETS) in 2015. These algorithms have also been published in Clinical and Applied Thrombosis/Hemostasis in 2014.[2]

The discussion of GIB was a natural step within the Share Network Group. In 2019, a multidisciplinary team with most Share Network members and some Transfusion Medicine and Gastroenterology experts gathered to discuss the condition. The present book reflects the opinion of this multidisciplinary team of Anesthesiology, Gastroenterology, and Transfusion Medicine physicians with expertise in the management of patients with GIB.[1] Its main purpose is to provide clear and objective guidance based on interventional algorithms, towards a goal-directed approach based on current knowledge.[1] Through these algorithms, physicians from big hospitals but also from small centers and primary clinics will be able to diagnose, manage, and treat GIB, practicing a value-based healthcare. The importance of a multidisciplinary approach for the quality of care provided to patients is emphasized.

The algorithms in this book have been presented in several webinars and meetings organized by the Portuguese scientific societies of Anesthesiology, Gastroenterology, and Transfusion Medicine and sponsored by CSL Behring, and have been published in Clinical and Applied Thrombosis/Hemostasis 2020.[1]

CSL Behring supported all the Share Network Group work and made this project possible, and the authors sincerely acknowledge this contribution.

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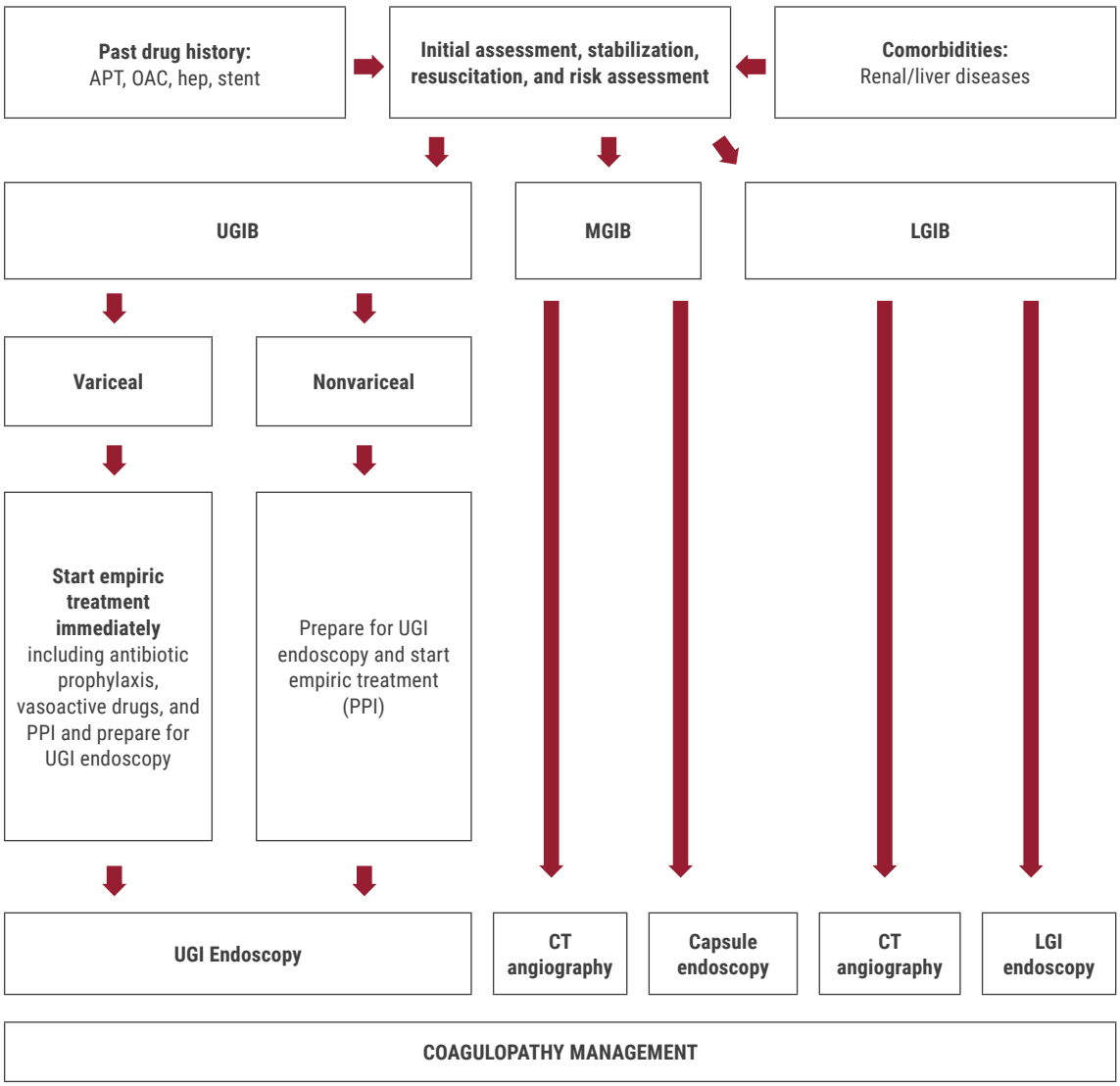


APT, antiaggregant platelet therapy; CT, computerized tomography; hep, heparin; LGI, lower gastrointestinal; LGIB, lower gastrointestinal bleeding; MGIB, middle gastrointestinal bleeding; OAC, oral anticoagulant; PPI, proton pump inhibitor; UGI, upper gastrointestinal; UGIB, upper gastrointestinal bleeding.

**Figure 1.** Gastrointestinal bleeding management algorithm

# Methods

On February 2019, a group of 14 advisors assembled in three working groups according to their areas of expertise — Transfusion Medicine (n=5), Anesthesiology (n=4), and Gastroenterology (n=5) — gathered to issue a global and personalized approach statement to the management of patients with gastrointestinal bleeding (GIB) according to different clinical practice settings. The aim was to develop a series of interventional algorithms that enabled an easy and practical GIB control based on a multimodal and multidisciplinary approach. Each group of experts was assigned the consensus of the corresponding area of expertise. A comprehensive literature review about the available published data on each topic was conducted on PubMed database using the keywords "gastrointestinal bleeding", "algorithm", "coagulopathy", "blood management", "transfusion", "goal-directed therapy", "coagulation", "variceal", and "nonvariceal." Based on the retrieved evidence, each working group independently developed the corresponding algorithms, which were finally assembled in one manuscript that was shared, reviewed, and approved by all advisors.[1]

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# Initial evaluation and stabilization

## Alexandre Carrilho, Mário Jorge Silva, Pedro Duarte

Gastrointestinal bleeding (GIB) encompasses bleeding originating anywhere in the gastrointestinal tract and is a common medical emergency worldwide. In a recent study, overall in-hospital mortality was around 10% (7% in hospital admissions due to GIB, and as high as 26% if bleeding occurring for other causes during hospitalization).[1]

Traditionally, GIB was classified into upper GIB (originating from the esophagus to the ligament of Treitz, at the duodenojejunal flexure) and lower (originating from a distal site to the ligament of Treitz) GIB. More recently, upper GIB was redefined as bleeding originating above the ampulla of Vater (within reach of an upper endoscopy) and lower GIB has been further subdivided into mid GIB (arising from the small bowel between the ampulla of Vater and the terminal ileum) and lower GIB (arising from the colon).[2] This chapter refers to *overt* GIB, which presents with clinical manifestations of bleeding, in opposition to occult GIB, which usually refers to microscopic hemorrhage presenting with occult blood loss in stool, with or without iron-deficiency anemia.[2]

The initial approach to the patient presenting with more than minimal GIB includes simultaneous clinical/laboratory patient evaluation and hemodynamic/cardiorespiratory stabilization, with urgency depending on blood loss volume and repercussion.[3] The *Airway, Breathing, Circulation, Disability, Exposure* (ABCDE) approach is generally suggested to all critical patients.[4]

A multidisciplinary approach including Surgery, Anesthesiology, Gastroenterology, Transfusion Medicine, Intervention Radiology, and Intensive Care Medicine is preferred, particularly for management of unstable patients, and obviously depending on locally available resources and protocols.

Clinical evaluation is decisive to identify potential bleeding causes, estimate the volume of blood loss and assess its repercussion,[3] detect contraindications to specific procedures (e.g., allergy to iodinated contrast, visceral perforation), and guide empiric medical therapy and diagnostic testing. Clinical assessmentalso enables risk stratification, identifying patients at particularly high risk and those who can be discharged and further studied as outpatients (through Glasgow Blatchford Score for upper GIB and Oakland score for lower GIB, for instance).

Upper GIB usually presents with hematemesis (vomiting of fresh blood), “coffee-ground” emesis (vomiting of dark altered blood), and/or melena (black tarry stools).[2] Hematochezia

(passing of red blood from rectum) usually occurs with lower GIB, but can occasionally be the presentation of brisk upper GIB.[2] Bleeding from the right colon or small intestine, on the other hand, may present with melena.[2] It is important to identify signs of active bleeding,[5] such as persistent hematemesis/melena/hematochezia, bright red blood in nasogastric tubing, and hemodynamic instability. Digital rectal examination may be very informative when stool characteristics are not evident.[3] In patients presenting with hematochezia and significant hemodynamic impact, an upper GIB source should be considered.[6]

Other presentations that may accompany GIB include abdominal pain, hemodynamic instability, and symptoms of anemia, as lethargy, fatigue, syncope, and angina.[2]

Past medical history may identify risk factors for specific bleeding causes, such as previous history of GIB, history of liver cirrhosis/portal hypertension, abdominal aortic aneurism/aortic graft, or medications such as nonsteroidal anti-inflammatory drugs (NSAIDs; predisposing for peptic ulcer disease).[7,8] Assessment of comorbid illnesses may identify patients particularly susceptible to the effects of anemia (e.g. cardiovascular disease), at risk due to impact of volume overload during resuscitation (e.g. heart failure, renal failure), with impaired clotting (e.g. coagulopathies), or with increased risk of aspiration (e.g. encephalopathy, dementia).[8] Pharmacological history may identify predisposition to particular bleeding causes (e.g. NSAIDs) and cases of medication-induced impaired hemostasis (e.g. antiplatelet agents and anticoagulants).[8] Early identification or suspicion of portal hypertension is particularly important, as specific measures (as use of vasopressors and antibiotic prophylaxis) are recommended in such cases.

Vital signs should be evaluated and monitored according to clinical severity, installation speed, and hospitalization level.[9] It is difficult to quantify blood loss in GIB. In an early phase, normal hemoglobin values (as hemodilution has not yet occurred) and normal blood pressure (due to vasoconstriction, compensatory increased cardiac contractility, and tachycardia) do not exclude significant hemorrhage.[5] Tachycardia is a better early sign of severity,[5] obviously interpreted with particular caution in patients with rate-lowering heart medications (e.g. β-blockers).

| Table 1: Clinical classification of severity of post-hemorrhagic hypovolemic shock[1] | | | | |
|---|---|---|---|---|
| **Feature** | **Class I** | **Class II** | **Class III** | **Class IV** |
| Blood loss | | | | |
| (mL) | <750 | 750-1500 | >1500-2000 | >2000 |
| (%) | <15 | 15-30 | >30-40 | >40 |
| Heart rate (beats/minute) | <100 | >100 | >120 | >140 |
| Blood pressure | Normal | Normal | Decreased | Decreased |
| Pulse pressure | Normal | Decreased | Decreased | Decreased |
| Respiratory rate (breaths/minute) | 14-20 | 20-30 | 30-40 | >40 |
| Urinary output (mL/hour) | >30 | 20-30 | 5-15 | Negligible |
| Mental status | Slightly anxious | Mildly anxious | Anxious, confused | Confused, lethargic |
| Fluid replacement (mL/hour) | Crystalloid | Crystalloid/colloid | Crystalloid and blood | Crystalloid and blood |

Some classifications have been proposed to estimate blood loss based on clinical parameters.

Laboratory tests in GIB setting include crossmatch and other pre-transfusional tests, complete blood count, coagulation studies (including viscoelastic tests, when available), and liver and renal biochemistry. As stated earlier, hemoglobin may be within patient baseline levels in an early phase of major GIB. Microcytic red blood cells suggest chronic bleeding. Elevated blood urea nitrogen (BUN) to serum creatinine ratio (>30:1) or urea-to-creatinine ratio (>100:1) suggests an upper GIB site.[8]

As the patient is evaluated, resuscitation measures are simultaneously started according to the ABCDE approach. The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent organ failure.[11] The first key step is hemodynamic stabilization, crucial for subsequent diagnostic and therapeutic management. The need for Intensive Care Unit admission should be early assessed.[5]

With the aim of maintaining partial pressure of oxygen ($PaO_2$) >60 mmHg and oxygen saturation ($SaO_2$) >90%, pulse oximetry should be monitored, and oxygen supplementation initiated to increase oxygen delivery to tissues and decrease pulmonary vasoconstriction resulting from the hypoxia state. Evolution to respiratory failure should be anticipated in patients in shock with metabolic acidosis. Orotracheal intubation should be considered to protect the airway in cases of persistent hematemesis or depressed consciousness level.[9]

In patients with GIB, a decrease in systolic blood pressure (SBP) greater than 10–20 mmHg or an increase in heart rate (HR) greater than 15 beats per minute, with change of position, suggests hypovolemia[12]. Paleness, cold extremities, oliguria, and altered mental status generally accompany sustained hypotension (SBP <90 mmHg or mean blood pressure [MBP] <65 mmHg) and indicate life-threatening blood loss. The shock index (SI=HR/SBP) is a marker of active bleeding and identifies unstable patients when its value is greater than 1.[1] A SI ≥1 can also be used to predict contrast extravasation during angiography, with the patient more likely to benefit from computerized tomography angiography (CTA) for identification of the bleeding site and planning subsequent measures.[13,14]

Large bore peripheral venous access is required, with at least two 16–18 gauge intravenous cannulas.[5] Early resuscitation should be initiated in hemodynamically unstable patients, generally with crystalloids, although some uncertainty remains regarding the type, amount, and rate of fluid resuscitation.[6,11]

Patients should be initially kept on nil by mouth. Nasogastric/orogastric intubation is not routinely recommended in acute upper GIB, either for aspiration or lavage, as it proved suboptimal in distinguishing upper from lower GIB and failed to improve stomach visualization in endoscopy and several clinically relevant outcomes. Consequently, its use should be evaluated on a case-by-case basis.[15]

In the context of upper GIB, other recommended measures include intravenous erythromycin in prokinetic dosing prior to endoscopy and proton-pump inhibitors.

# Recommended measures

- Consider $O_2$ supplementation and orotracheal intubation to protect the airway in cases of persistent hematemesis or change in consciousness level.
- Insert two peripheral venous accesses of 16–18 gauge.
- Collect blood samples to assess complete blood count, coagulation, biochemistry, pre-transfusional tests, and viscoelastic tests (VET), when available.
- Start resuscitation with crystalloids (1L of polyelectrolytic solution).
- Provide 2–4 packed red blood cells (PRBCs) in cases of severe bleeding and absence of hemodynamic recovery with crystalloids.
- Assure normovolemia and normothermia.
- Assure nill by mouth.
- Nasogastric/orogastric intubation is not recommended on a routine basis.[15]

# Other considerations

- Administration of blood and blood products should be performed according to hemodynamics, clinical monitoring, viscoelastic test (ROTEM®) result, and laboratory results.
- In unstable patients, arterial line should be placed for direct blood pressure monitoring, conducting gasimetry and serial laboratory tests periodically and monitoring the urine output hourly.
- A central venous catheter should be placed to determine the central venous pressure and monitor central venous oxygen saturation ($SvO_2$), if possible, without interfering with stabilization and diagnostic measures.
- In ventilated patients with sinus rhythm, analysis of pulse wave through assessment of the variation in pulse pressure or stroke volume is more sensitive for analysis of response to the implemented fluid therapy than central venous pressure (CVP).
- Transthoracic echocardiography provides information on venous return, filling of the pulmonary artery, cardiac output, and cardiac function.
- Minimally noninvasive hemodynamic monitoring by esophageal doppler or skin reactance allows an adequate continuous analysis of response to the implemented therapy.

- Continuous monitoring of oxyhemoglobin (Masimo Technology) allows continuous monitoring of hemoglobin values and peripheral perfusion index, warning to the occurrence of sudden invisible blood loss. However, it does not waive laboratory evaluation.

# Hemodynamic objectives of the implemented therapy[12]

- MBP between 65 and 90 mmHg
- CVP between 5 and 12 mmHg
- Cardiac index between 2 and 4 L/min/$m^2$
- $SvO_2$ >70%

In absence of hemodynamic recovery following administration of crystalloids and erythrocyte concentrate, administration of noradrenaline at the initial dose of 0.1–0.2 mcg/Kg/min and until a maximum of 2 mcg/Kg/min should be considered to ensure MBP >65 mmHg.

Hemodilution should be avoided, and a permissive hypotension strategy chosen until bleeding is controlled.

Intraosseous access may be an alternative to central venous catheterization if peripheral venous catheterization is not achieved.

Transfusional support should be provided according to clinical evolution and laboratory results. Coagulopathy management should be preferably oriented by VET.[16,17]

Upper GIB should be considered in presence of hematochezia associated with significant hemodynamic instability.[13] In patients with chronic liver disease (CLD), portal hypertensive cause of GIB should be considered and specific measures early initiated (even before etiologic confirmation), including vasopressor therapy and prophylactic antibiotherapy.

# Correction of anemia and coagulopathy

In patients presenting with GIB, prompt diagnosis of the hemorrhage site and cause should be ensured.

In acute hemorrhage, the hematocrit may not reflect anemia severity. In early stage of GIB, a normal hemoglobin value does not exclude major bleeding. Anemia causes a decrease in arterial oxygen content and in the release of oxygen to tissues.

# Massive bleeding protocol should be activated in cases of blood loss:

a) equivalent to 100% of volume in 24 hours

b) equivalent to 50% of volume in 3 hours

c) at a rate of 150 mL/min in adults

# Therapeutic objectives[18]

- Stop bleeding.
- Maintain hemoglobin between 7 and 9 g/dL (>9 g/dL in patients with ischemic heart disease).
- Prevent coagulopathy.
- Avoid hemodilution, hypothermia, acidosis, and hypocalcemia (coagulopathy aggravating factors).

Transfusion support should be based on clinical evolution and laboratory results (hemoglobin, platelet count, prothrombin time/international normalized ratio [PT/INR], activated partial thromboplastin time [aPTT], fibrinogen, and/or viscoelasticity tests – ROTEM®/ TEG®).

# Therapeutic attitude

- Hemoglobin <7 g/dL – Administer erythrocyte concentrate at 2 to 4 U
- Platelet count less than 50,000 /µl – Administer a pool of platelet concentrate
- Fibrinogen <1.5 g/L – Administer 2 to 4 g of fibrinogen concentrate
- INR >1.5 and/or PT and PTT >1.5 times the normal value – Administer prothrombin complex concentrate or fresh frozen plasma

# Poor prognostic factors

a) Temperature <35ºC

b) $PaO_2$ <60 mmHg

c) $SaO_2$ <90 mmHg

d) $SvcO_2$ <65 mmHg

e) pH <7.2

f) Base excess >-6

g) Lactate >4 mmol/L

h) Ionized calcium <1.1 mmol/L

i) Platelet number <50,000/µl

j) PT/INR >1.5 x normal

k) aPTT >1.5 x normal

l) Fibrinogen <1.5 g/L

# Coagulopathy correction according to thromboelastometry (ROTEM®)

## HYPERFIBRINOLYSIS

EXTEM CT > APTEM CT
EXTEM ML >15%

↓

Tranexamic acid 1 g, iv, in 10 minutes
Alternative: Aminocaproic acid, 4–5 g iv

### FIBRINE DEFICIT

FIBTEM CA10 <7 mm
FIBTEM MCF <9 mm

↓

Fibrinogen concentrate, 2–6 g
Alternative: Cryoprecipitates or fresh frozen plasma

### DEFICIT OF OTHER FACTORS

EXTEM CT > 80 s
INTEM CT > 240 s

↓

Prothrombin complex concentrate, 20 $U/Kg^{-1}$
Alternative: Fresh frozen plasma (10 to 20 mL/kg)

### PLATELET DEFICIT

EXTEM CA10 <40 mm
and FIBTEM CA10 >12 mm
Platelet count <50,000/µl

↓

Platelet concentrate pool

### DANGEROUS COAGULOPATHY

EXTEM CA10 <30 mm

↓

Tranexamic acid 1 g, iv, in 10 minutes
Fibrinogen concentrate, 6–8 g
Prothrombin complex concentrate, 20–30 $U/Kg^{-1}$
Platelet concentrate pool

APTEM, activation of clot formation by cytochalasin D; CA10, amplitude at 10 minutes; CT, coagulation time; EXTEM, activation of clot formation by thromboplastin; FIBTEM, activation of clot formation by aprotinin; g, gram; INTEM, activation of clot formation via the contact phase; iv, intravenous; Kg, kilogramme; MCF, maximum clot firmness; ML; maximum lysis; mL, milliliter; mm, millimeter; S, second; U, unit; µl, microliter

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## Clinical presentation[13,15]

Signs of active bleeding? (hematemesis, melena, hematochezia*, fresh blood on nasogastric tube, syncope, hemodynamic instability, others)

*Hematochezia + hemodynamic instability: consider UGIB

## Immediate evaluation/stabilization[13,15]

- **Shock Index (SI=HR/SBP), with restrictions in specific situations (e.g. β-blocker therapy)**
- **Simultaneous evaluation and resuscitation measures**

- **ABCDE approach, depending on clinical case:**
  **A:** ***Airway:*** Look for airway patency and stability
  - consider orotracheal Intubation in cases of massive bleeding, decreased level of consciousness, risk of aspiration of gastric content, others…

**B:** ***Breathing:*** Respiratory Rate, $SpO_2$:consider $O_2$ supplementation

**C:** ***Circulation:***

- Non-invasive monitoring of BP, HR (tachycardia is an early indicator), and urine output
- Insert 2 peripheral venous lines (16-18 g)
- Collect blood sample: FBC, PTT, CS (PT, aPTT, Fib), VET, biochemistry, ABG
- Give warm fluid crystalloids (polyelectrolytes); PRBC in cases of severe bleeding or no response to crystalloids
- Further blood transfusion should be goal-directed by targets (see below)
- Estimate blood loss: Important to quantify
- Consider CVC
- Consider dynamic ultrasonographic evaluation of the inferior vena cava
- Correct metabolic + electrolyte imbalances and other perfusion indexes

**D:** ***Disability:*** neurological state of consciousness and collaboration body warmers, warm blankets, heating environment.

**E:** ***Exposure:*** attention to room and body temperature. Keep normothermia: consider blood + iv fluids + body warmers, warm blankets, heating environment.

- **Nasogastric/orogastric intubation is not routinely recommended[15]**
- **Nill by mouth**
- **AVOID: Fluid overload and excessive transfusion**

**Severe**

## SI ≥1: Severe bleeding

**Consider (according to clinical picture and availability):**

- CT with angiogram
- Massive bleeding protocol activation
- Insert arterial + venous catheters
- If no hemodynamic response to crystalloids + PRBCμ give noradrenaline: 0.1–0.2μg/Kg/m (maximum 2 μg/Kg/m) if MAP not recovered
- Transfer to the ICU: instability, comorbidities, other risks conditions…

## Multidisciplinary approach

*According to clinical scenario andclinical team:*

*Gastroenterology, Transfusion Medicine, Anesthesiology, Surgery, Intervention Radiology, Intensive Medicine, …*

| Past medical history (see alg.2) | Past drug history (see alg. 2) |
|---|---|
| **Clinical Evaluation – History of:**<br>• Previous GIB, known gastrointestinal (GI) disease or prior GI surgery; recent digestive endoscopy<br>• Radiotherapy<br>• Aortic surgical/endovascular therapy, aortic aneurism (-> aortic fistula)<br>• Previous vomiting before bleeding? (→ Mallory-Weiss)<br>• Severe abdominal pain (→ ischemia, GI perforation)<br>• Wasting syndrome (→ neoplasia)<br>• Comorbidities: chronic liver, renal and ischemic heart disease; coronary stent | **Drugs that interfere with coagulation:**<br>• Anticoagulants<br>• APT<br>• NSAID |

| Laboratory investigation<br>According to clinical picture | Other exams (before endoscopy)<br>According to clinical picture |
|---|---|
| • FBC and CS (PT, aPTT, Fibrinogen), VET (according to bleeding severity)<br>• BUN, creatinine → BUN/creatinine ratio [(BUN mg/dl)/(creatinine mg/dl)] > 30 indicates that urea is disproportionately high, meaning low renal perfusion or blood in small bowel<br>• Glucose, ionogram, $Ca^{++}$, phosphate, magnesium, CRP, hs-cTnI<br>• AST, ALT, bilirubin, albumin<br>• Pre-transfusional tests[17], - reserve / transfuse PRBC<br>• ABG: if severe clinical status - estimate Hb, acid-basis + lactate<br>• Monitor every 30-60m or according to bleeding severity: ABG, FBC, CS, iCa17,19 | • ECG, chest x-ray (individualized)<br>• Urgent fluoroscopic/CT angiography in patients with history suggestive of aorto-enteric fistula, severe bleeding refractory to hemodynamic stabilization, persistent bleeding with negative upper endoscopy and not responding to hemodynamic stabilization measures, suspicion of visceral perforation, other individualized conditions |

**RESUSCITATION (Hemodynamic stabilization - severe bleeding)**

| | Hemodynamic[18,20] | Therapeutic[16,17] | Laboratory values[18,20,21] | Tranfusional Therapy (see alg.4) | | Poor prognostic values[17] |
|---|---|---|---|---|---|---|
| TARGETS | • MAP: 65–90 mmHg<br>• Heart Index: 2–4 L/m/m²<br>• SaO2 >92%<br>• SvO2 >70%<br>• Temperature | • Stop bleeding<br>• Correct anemia<br>• Avoid: coagulopathy, hemodilution, hypothermia, acidosis, hypocalcemia<br>• Correct coagulopathy guided by VET (see Alg.[4]) | • Hb: 7–9 g/dL<br>• Htc >24–28%<br>• Platelets >50x109/L<br>• Fibrinogen >2.0g/L<br>• INR/PT/aPTT <1.5 x NV<br>• In Severe Bleeding:<br>– $Ca^{++}$ >1.2 mmol/L<br>– pH >7.2<br>– Lactate <4mmol/L<br>– Base Deficit <-3<br>**Endoscopic approach is not dependent on complete correction until target values are reached** | • Hb <7 gr/dL→ PRBC<br>• Platelets <50.000/ → PC<br>• Fib. <1.5–2-0 g/L → FC<br>• INR >1.5 /PT/aPTT >1.5 → PCC/ FFP | ALERT | • Temperature <35ºC<br>• Base deficit > -6 mmol/L<br>• pH <7.2<br>• Lactate >4mmol/L<br>• $Ca^{++}$ <1.1mmol/L<br>• PaO2 <60mmHg<br>• Sat.O2<90mmHg<br>• Platelets <50x109/L<br>• Fibrinogen <1.5 g/L<br>• INR >1.5 /PT/aPTT > 1.5x NV |

ABCDE, Airway, Breathing, Circulation, Disability, Exposure; ABG, arterial blood gases; Alg, algorithm; ALT, alanine aminotransferase; aPTT, acti\vated partial thromboplastin time; AST, aspartate aminotransferase; BP, blood pressure; BUN – Blood Urea Nitrogen $Ca^{++}$, calcium; CT, computerized tomography; CVC, central venous catheter; ECG, electrocardiogram; FBC, full blood count; FC, fibrinogen concentrate; FFP, fresh frozen plasma; Fib, fibrinogen; GI, gastrointestinal; GIB, gastrointestinal bleeding; Hb, hemoglobin; hs-cTnI, high-sensivity cardiac troponin; HR, heart rate; Htc, hematocrit; ICU, Intensive Care Unit; iCa+, ionized calcium; INR, international normalized ratio; iv, intravenous; m, minute; MAP, median arterial pressure; NSAID, nonsteroidal anti-inflammatory drug; NV, normal value; $O_2$, oxygen; APT, antiaggregant platelet therapy; PC, platelet concentrate; PCC, prothrombin complex concentrate; CRP, c-reactive protein; PRBC, packed red blood cell; PT, prothrombin time; PTT, pre-transfusional test; SBP, systolic blood pressure; SI, shock index; UGIB, upper gastrointestinal bleeding; VET, viscoelastic tests

**Algorithm 1.** Initial assessment and resuscitation.

# Potentially aggravating factors in gastrointestinal bleeding

# 1. Comorbidities

**Alexandre Carrilho**

One of the biggest challenges in the management of gastrointestinal bleeding (GIB) is the aging of the population and its comorbidities. Aggravating factors of GIB include liver failure, renal failure, antithrombotic therapy, and cardiovascular disease.

## 1.1. Liver failure

Liver disease (LD) is associated with decreased clearance of proteins involved in fibrinolysis, decreased production of coagulation factors (vitamin K dependents, fibrinogen, FV, FXIII) and natural anticoagulants (proteins C and S, antithrombin), dysfibrinogenemia, low platelet count/impaired platelet function, and increased FVIII/von Willebrand factor (vWF).[1] This increase in vWF levels can partially compensate the thrombocytopenia that frequently occurs in cirrhotic patients, preserving primary hemostasis.[1] Patients with cirrhosis also have an increased risk of thrombosis.[1] In the context of variceal hemorrhage, over-resuscitation may aggravate bleeding by markedly increasing blood pressure. The use of plasma – associated with fluid overload and portal venous pressure increase – should be avoided.[1,2] Based on the latest data, hepatic coagulopathy should be managed with coagulation factor concentrates (CFC) rather than plasma, as the first are more effective and have fewer side effects in volume overload and/or infections.[1]

# 1.2. Renal failure

GIB in patients with impaired kidney function is associated with high mortality risk. The main causes of hemorrhage in these patients are peptic ulcer, gastritis, duodenitis, angiodysplasias, and systemic vasculitis.

In chronic renal failure, anemia results from the inhibition of erythropoiesis due to absence of erythropoietin synthesis, reduction in erythrocyte life cycle, hemolysis during dialysis, and hemorrhagic complications (ecchymosis, petechiae, digestive hemorrhage, etc.).

Elevated levels of urea and other toxins promote platelet dysfunction and reduce their ability to aggregate through:

- Alteration in vWF binding to glycoprotein Ib/IX.
- Decreased levels of thromboxane A2 and ADP.
- Increased levels of cAMP and cGMP (the latter stimulated by excess nitric oxide).
- L-arginine accumulation, with inhibition of platelet aggregation.

Thrombocytopenia is generally mild and due to friction produced by the extracorporeal circulation pump and changes in platelet structure and function, with a decrease in the number of granulations, serotonin deposits, and ADP.

The decrease in the number of red blood cells reduces platelet contact with the vascular wall. Platelet adhesion to the vascular wall is also compromised by an increase in prostaglandins (PGi2). In renal failure, packed red blood cell administration partly reverses the hemorrhage tendency. Administration of erythropoietin stimulates the production of erythrocytes and hemoglobin synthesis, requiring adequate iron, folate, and vitamin B12 supply.

In hemodynamic stabilization, adequate renal perfusion should be assured in patients with residual renal function, as well as hyperkalemia and volume overload monitoring. Anemia should be corrected to a hematocrit target of 30% (Grade 1C)[3] and low levels of fibrinogen should be corrected with fibrinogen concentrate. Desmopressin (0.3 mcg/Kg) induces the release of vWF into plasma and reduces bleeding time by approximately one hour.[4]

Given the association between urea levels and bleeding risk, patients with high uremia and bleeding generally benefit from dialysis without heparin.

Administration of tranexamic acid is not indicated in renal failure.[4]

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# 2. Antithrombotic therapy and gastrointestinal bleeding


## Luciana Ricca Gonçalves, António Robalo Nunes


Antithrombotic drugs – namely oral anticoagulants, heparins, and antiplatelet agents (APT) – are widely used in the treatment and prophylaxis of thrombotic events. The proportion of patients requiring long-term antithrombotic therapy is expected to rise considerably.[1-3] However, any antithrombotic treatment is associated with an increased risk of bleeding. Whereas the annual bleeding risk associated with anticoagulation is estimated in 2–4%, the risk of *major* bleeding in certain patient populations increases to as much as 15%/year.[4]

The approach to patients under antithrombotic therapy presenting with gastrointestinal bleeding (GIB) depends on the type of antithrombotic drug, GIB severity, and risk of thromboembolic events.[4-6]

## Patients on anticoagulation

Management of anticoagulation-associated bleeding has become increasingly challenging with the growing number of available drugs. Besides vitamin K antagonists (VKA), which are widely used, direct oral anticoagulants targeting either factor Xa (apixaban, edoxaban, rivaroxaban) or thrombin (dabigatran etexilate) are increasingly prescribed.[4-6]

In some clinical settings, patients can also be under heparin, namely low-molecular-weight heparin (LMWH). Reversal strategies are different according to the type of anticoagulant.

# 2.1. Patients on vitamin K antagonists

VKA antagonize the activation of procoagulant factors II, VII, IX, and X and anticoagulant proteins C and S, which are vitamin K-dependent coagulation factors produced in the liver. Vitamin K-dependent factors require a gamma-glutamyl carboxylase modification to accomplish their function in coagulation, which is inhibited by VKA, decreasing the amount of these functional factors.[9]

## Laboratory evaluation of the effect of VKAs

The anticoagulant effect of VKA is commonly assessed by a simple, one-step laboratory coagulation test – the prothrombin time (PT). PT evaluates the extrinsic (factor VII) and common (factors X, V, II, and I [fibrinogen]) coagulation pathways. For VKA therapy monitoring, PT is reported as international normalized ratio (INR). INR is calculated by dividing the patient's PT by the mean normal prothrombin time (MNPT) raised to the exponent (power) of the international sensitivity index (ISI). INR was introduced as a method to standardize the reporting of VKA-treated patient samples, as there was an unacceptably wide variability in PT values reported between laboratories, hindering comparison of patient results between them.[10-13]

Monitoring VKA anticoagulation through PT/INR allows the clinician to implement an appropriate management strategy.

# Treatment options for VKA reversal

VKA reversal is recommended in VKA users presenting with clinically significant acute GIB (hematemesis, melena, severe hematochezia causing acute anemia), as the risks of continued bleeding are supposed to outweigh those of thrombotic events.[5-7]

Several strategies are in place for VKA therapy reversal. These include VKA treatment interruption, administration of vitamin K (usually phytonadione), and administration of blood derivatives, such as prothrombin complex concentrate (PCC), fresh frozen plasma (FFP) and, as an end-line option, recombinant activated factor VII (rFVIIa) for life-threatening bleeding not responding to PCC.[5-7,14-18,21]

The chosen strategy should consider the clinical context (severity and evolution of bleeding and patient's hemodynamic stability), INR value on admission and VKA reversal urgency, timing of invasive procedures (e.g., endoscopy), if required, and patient's thrombotic risk.

# Vitamin K

Vitamin K is used as a VKA reversal agent for its ability to restore the intrinsic hepatic synthesis of vitamin K-dependent clotting factors, overcoming VKAs in a dose-dependent manner.[7,14] It can be given orally or intravenously. In stable patients without indication for urgent reversal, VKA interruption and low doses of oral vitamin K can be considered, with an expected reduction in the INR within 18–24 hours.[14]

In bleeding patients, higher doses of intravenously administered vitamin K (5–10 mg) act more rapidly, reducing INR in 4–8 hours. However, this timing depends on the patient's underlying hepatic function.[6,14,19] It is advised to test INR within 8–12 hours after vitamin K administration. A repeat dose of 5–10 mg may be considered when INR values remain elevated.[20] Intravenous (iv) administration should be slow, in 25–50 mL normal saline over 15–30 minutes, to minimize the anaphylactic risk.

Vitamin K does not result in immediate coagulopathy correction, but provides a sustained coagulopathy correction that lasts beyond the one provided by administration of coagulation factors (FFP or PCC).[5-7,14]

In patients with major bleeding requiring urgent reversal, vitamin K-dependent coagulation factors should be given, specifically prothrombin complex concentrate (PCC) or fresh frozen plasma (when PCC is unavailable).[5-7,14,21]

## Frozen fresh plasma

FFP remains a widely used reversal strategy for urgent VKA reversal. One plasma unit (approximately 200 mL) is usually obtained from whole-blood donation or by apheresis donation. FFP contains vitamin-K–dependent clotting factors, but also other coagulation factors and proteins, being considered a nonspecific reversal agent.

Because one unit of any given factor is present in 1 mL of normal pooled plasma, adequate plasma for VKA reversal should be 15 to 30 mL/kg. However, the volume of plasma at this dose is not practical for rapid VKA reversal in most patients. Therefore, the recommended dose is an iv infusion of 15 mL/Kg.[14]

FFP has several limitations: significant time is required for ABO blood group match and to thaw plasma units; the administration of a large FFP volume increases the time required to correct INR and puts patients at risk of fluid overload; and FFP may be associated with transfusion-related acute lung injury (frequency of 1 in 5,000 plasma-containing transfusions)[14] and carries the risk (although minimal) of transmission of infectious agents, as most FFP products are not virally inactivated. The time to FFP effect is 10 minutes, but it takes a few hours for partial INR reversal and at least 9 hours for complete reversal (i.e., INR <1.5). Warfarin reversal efficacy is supported by moderate evidence only.[16]

## Prothrombin complex concentrate

PCC is the first-line therapy for urgent VKA reversal.[17] PCC is obtained from pooled human plasma and contains lyophilized purified vitamin K-dependent clotting factors (factors II, IX, X, and variable amounts of factor VII). Inactivated PCC is classified as 3F- or 4F-PCC according to factor VII concentrations: 3F-PCC contains adequate levels of factors II, IX, and X and low levels of factor VII; 4F-PCC contains adequate levels of factors II, VII, IX, and X, as well as of proteins C and S. Both PCCs contain non-activated factors and require *in vivo* activation. 3F-PCC is less effective than 4F-PPC for warfarin reversal, due to persistent factor VII deficiency.[15,18,23] 4F-PCC contains approximately 25 times (25 U/mL) the concentration of vitamin K-dependent factors per unit volume compared with plasma (1 U/mL). Only 4F-PCC is licensed for urgent VKA reversal.

The amount of each vitamin K-dependent factor varies and is listed on every vial. PCC is standardized according to respective factor IX content. It is administered intravenously, usually at the dose of 25–50 IU/Kg, depending on the baseline INR. Administration of PCC results in rapid anticoagulation reversal, which is demonstrated by PT/INR normalization.

PCC presents several advantages over FFP: it is virally inactivated, do not require crossmatch, and can be stored lyophilized at room temperature. Consequently, these products can be rapidly reconstituted into a small volume and infused over 15 to 30 minutes without risk of volume overload, leading to fast INR correction.[14,15,22,24-26]

Concerns have been raised regarding the occurrence of thromboembolic events with PCC. While the risk of thrombosis is minimized by adding heparin and antithrombin in non-activated PCC composition, it still needs to be considered. However, recent randomized clinical trials comparing nonactivated 4F-PCC with plasma for VKA reversal showed a similar incidence of thromboembolic event in both groups.[27,28]

In comparison, activated PCC products contain inactivated factors II, IX, and X and activated FVII.[17] They can bypass deficient or inhibited factors and are used for the treatment of bleeding in patients with hemophilia A with inhibitors.[29]

## Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) is structurally similar to native FVIIa, promoting hemostasis by activating the extrinsic pathway. Evidence of rFVIIa effectiveness in VKA reversal in severe bleeding is limited to case reports and small case series.[30]

However, the use of both rFVIIa and factor eight inhibitor bypass activity (FEIBA) is associated with a higher risk of thrombotic events. None of these agents is licensed for this indication and their routine use should be avoided.[31,32]

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# 2.2. Patients on direct oral anticoagulants

Direct oral anticoagulants (DOACs; dabigatran etexilate, rivaroxaban, apixaban, and edoxaban) have become widely used since their approval for several cardiovascular conditions, including prevention and treatment of venous thromboembolism (VTE) and prevention of stroke in non-valvular atrial fibrillation (NVAF). DOACs act as anticoagulants by inhibiting specific serine proteases: dabigatran inhibits free and fibrin-bound thrombin by binding to the thrombin active site, and apixaban, edoxaban, and rivaroxaban are direct reversible inhibitors of factor Xa. DOACs present a more predictable pharmacokinetic and pharmacodynamic profile than vitamin K antagonist (VKAs) and are administered in fixed-dose regimens according to the indication, patient characteristics (age, body weight, renal function), and use of concomitant drugs.[1-5]

## Laboratory evaluation of the DOACs anticoagulation effect

Due to the above-mentioned features, routine coagulation monitoring is usually not required for DOACs.[6] However, assessment of their anticoagulant effect may be necessary in some clinical settings, including emergency ones, as prior to urgent invasive procedures and in patients presenting with acute major bleeding or thrombotic events. These tests are also important in cases of suspicion that DOAC level may be out of the expected range, as occurs in patients with renal or hepatic failure, suspected overdosing, extreme weight, malabsorption, or potential drug interactions.[7-11]

The maximal DOAC effect is reached within 2–3 hours of drug intake. These drugs have shorter half-lives than VKAs (between 5–14 hours) but are dependent on patients' renal and, to a lesser extent, hepatic function. For interpretation of coagulation assays in patients under DOACs, the timing of the last drug administration in relation to blood sampling and the evaluation of renal function are very important.[8-9]

The anticoagulant effect of DOACs can be assessed by qualitative and quantitative assays.

## Qualitative assays for DOACs

Due to the direct inhibition of thrombin or FXa, DOACs can interfere with most clot-based hemostasis tests, like prothrombin time (PT) and activated partial thromboplastin time (aPTT). However, DOAC assays have a wide range of sensitivity to each DOAC, depending on the reagent, equipment, and drug, as well as wide interindividual variability.[9]

## Direct thrombin inhibitor – Dabigatran

aPTT is prolonged in a nonlinear relation with increasing dabigatran concentrations. This assay can provide qualitative assessment of dabigatran activity, but its sensitivity depends on the reagents and equipment used.[8,9,12,13] Most dabigatran-treated patients have prolonged aPTT. A normal aPTT excludes on-therapy dabigatran levels but does not exclude the presence of dabigatran in the therapeutic range in approximately 20% of patients.

Thrombin time (TT) is highly sensitive to dabigatran and not affected by direct anti-Xa inhibitors. A normal TT value excludes anticoagulant activity, but a prolonged TT value is not

necessarily indicative of a high dabigatran level: TT is prolonged even with sub-therapeutic concentrations.[8,9,13-15] Both aPTT and TT have been used in dabigatran-treated patients in emergency situations to exclude relevant remaining anticoagulant effect and guide decisions regarding urgent interventions.

Dabigatran prolongs PT in a concentration-dependent manner. Variability among reagents in this assay is wide, and PT and the international normalized ratio (INR) are considered poorly sensitive to dabigatran.[8,9]

## Direct factor Xa inhibitors – Apixaban, edoxaban, and rivaroxaban

Apixaban prolongs PT and aPTT only at supratherapeutic concentrations.[8,9] PT may be normal with apixaban concentrations up to 200 ng/mL[16-18] and is not recommended for estimating apixaban concentrations, except in cases of suspicion of supratherapeutic concentrations.

Edoxaban prolongs PT and aPTT in a variable way.[8,9,18] PT is more sensitive than aPTT but has suboptimal sensitivity at low drug levels. For most reagents, PT is prolonged only at peak levels.[19] Both tests are not suitable for routine clinical assessment of edoxaban anticoagulant effect.

Rivaroxaban prolongs PT in a concentration-dependent manner, but response varies according to the thromboplastin used as reagent.[8,9,16,18,20] Only when sensitive reagents are used is PT prolonged both at trough and peak levels. If less sensitive reagents are used, PT is prolonged only at peak levels or when drug accumulation occurs. aPTT is prolonged in a nonlinear manner with increasing rivaroxaban concentrations, having lower sensitivity to rivaroxaban than PT.[8,9]

There is not enough data to support the use of thromboelastography-TEG® or thromboelastometry-ROTEM® for detecting DOAC anticoagulant activity.[9,21-23] Urine DOAC screening tests have been developed to provide a rapid assessment of DOAC exposure. However, they do not provide information about the presence of circulating drug or its concentration.[9,24]

## Quantitative assays

Specific tests to quantify DOAC are required in several settings.

The most accurate way of assessing DOAC exposure is by measuring drug concentration using liquid chromatography-mass spectrometry (LC-MS) or drug-calibrated clot-based or chromogenic methods.[9,25,26] LC-MS/MS testing is not available in most laboratories and is mainly used in clinical research. Drug-calibrated clot-based or chromogenic methods are commercially available and easily adaptable to automated coagulation analyzers.

## Dabigatran

Methods for quantifying dabigatran include diluted thrombin time (dTT), ecarin-based methods (ecarin clotting time [ECT], ecarin chromogenic assay [ECA]), and chromogenic anti-FIIa [C-FIIa] assay).[8,9,27] Dabigatran calibrators must be used to obtain a good correlation with dabigatran concentrations.

Commercially available dTT measures clotting time after addition of thrombin to diluted plasma samples. There is a linear correlation between clotting time and drug concentration, with good accuracy for concentrations between <50 and 500 ng/mL.[28]

Ecarin-based assays provide a direct measure of dabigatran activity. Ecarin is a metalloprotease from a viper venom – Echis carinatus – that converts prothrombin to meizothrombin, which is inhibited by direct thrombin inhibitors (DTIs) but not heparin.[29]

ECT test results have a linear correlation with LC-MS/MS dabigatran concentration measurements.[29] However, due to lack of standardization and limited availability, ECT testing is not recommended.[8,9]

ECA uses prothrombin, ecarin, and a chromogenic substrate specific for thrombin cleavage. Results from this assay have a good correlation with LC-MS/MS, being able to detect low dabigatran concentration levels (14–46 ng/mL, depending on the ECA chosen).[27,30]

Several commercial kits are available for quantifying dabigatran using chromogenic anti-FIIa assay (C-FIIa) methods similar to ECA. C-FIIa also has a good correlation with LC-MS/MS.[31]

## Direct factor Xa inhibitors

Chromogenic anti-Xa assays have been clinically used for assessing the anti-Xa activity of heparin anticoagulation. These assays are very sensitive to the presence of direct factor Xa (FXa) inhibitors.[8,9]

Anti-FXa assays calibrated with heparin standards can be used to exclude the presence of direct FXa inhibitors, but are affected by high inter-assay variability and should thus not be used to quantify anticoagulant effect.[32,33]

When anti-Xa assays with specific direct FXa inhibitor calibrators are used, a linear correlation is obtained between anti-Xa activity and anti-Xa DOAC, providing DOAC quantification results expressed in ng/mL.[8,9,34-36] These assays measure a wide range of plasma concentrations covering the expected therapeutic levels.

Overall, the low sensitivity and specificity of PT and aPTT to DOACs suggests that these tests have a poor, reagent-dependent ability to quantify DOAC concentration. However, in patients with known DOAC exposure, prolonged PT or aPTT should be considered secondary to drug effect until proven otherwise. In addition, these tests can help in the management of patient in emergent or life-threatening conditions, which is particularly important when the turnaround times of quantitative tests limit their use.

## Reversal of anticoagulation with DOACs

Reversal of anticoagulation with DOACs is facilitated by the short half-life of all these drugs. It is important to assess the exact time of the last DOAC intake and evaluate renal function. Impaired renal function prolongs DOAC half-life, especially dabigatran, which has a renal excretion of 80%. Laboratory evaluation of anticoagulant activity helps in the management of bleeding patients under DOACs. Selection of the best assay depends on the type of DOAC, assay availability, and clinical indication.[8,9,37]

Most bleeding complications associated with DOACs, including major gastrointestinal bleeding (GIB), can be managed by withholding the anticoagulant and providing supportive measures (fluid replacement and transfusions) to preserve the hemodynamic stability and enhance renal excretion.[38] In addition, most non-urgent invasive procedures can be temporarily delayed until the anticoagulant effect disappears.[39]

However, if urgent anticoagulation reversal is required, other measures must be taken and chosen according to the clinical situation. Recommendations include reduction of DOAC

absorption by oral administration of 50 g of activated charcoal, if DOAC ingestion occurred within the last 2–4 hours.[38-40] It is also important to promote DOAC excretion by increasing diuresis. As dabigatran displays low binding to plasma proteins (< 35%),[41] hemodialysis can be used to reduce its plasma concentration rapidly and efficiently (65% at 2–4 hours), particularly in patients with impaired renal function, in whom high levels of dabigatran are expected. However, hemodialysis is not effective for other DOACs that bind to plasma proteins at higher levels than dabigatran, as rivaroxaban, apixaban, and edoxaban.[38,42]

More aggressive reversal strategies are recommended in some clinical situations, including administration of specific or non-specific reversal anticoagulation agents (depending on the availability).[38-40]

## Specific anticoagulation reversal agents

Specific agents for DOAC reversal are already approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).

## Idarucizumab for dabigatran reversal

Idarucizumab is approved since 2015 for immediate anticoagulation reversal in dabigatran-treated patients with major or life-threating bleeding associated with hemodynamic instability or requiring urgent invasive procedures carrying increased bleeding risk. Idarucizumab is an antibody fragment (Fab) with an affinity to free or thrombin-binded dabigatran that is approximately 350 times that of dabigatran to thrombin.[43] The efficacy and safety of idarucizumab have been evaluated in the open-label REVERSE AD (Reversal of Dabigatran Anticoagulant Effect with Idarucizumab) trial.[44,45] In this trial, 503 dabigatran-treated patients in different emergency settings (either ongoing severe or life-threatening hemorrhage or emergency procedures on therapy) were given idarucizumab as a fixed-dose intravenous infusion of 2 x 2.5 g.[45] Maximum reversal of dabigatran anticoagulant effect, assessed by dTT or ECT, was achieved within 4 hours in all patients. Among bleeding patients, effect cessation was achieved within a median of 3.5–4.5 hours, depending on the hemorrhage location.[45] In patients undergoing procedures or surgery, hemostasis was normal in 93% during the procedure. Treatment with idarucizumab was safe, with no significant adverse effects. The rate of post-reversal thrombotic complications was 6%, and mortality rate was 13%.[45]

The administration of idarucizumab for dabigatran reversal in the event of life-threatening or uncontrolled bleeding is a Class I, Level of Evidence B recommendation in the 2019 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation.[46] Both the European Society of Cardiology and the European Heart Rhythm Association also recommend its use.[47] Idarucizumab is administered intravenously at the dose of 5 g given in two doses of 2.5 g no more than 15 minutes apart.

## Andexanet alfa for factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) reversal

Andexanet alfa is a recombinant protein similar to endogenous FXa but with no enzymatic activity that binds to FXa inhibitors. Andexanet alfa has been studied in the ANNEXA-4 (Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding) trial.[48] This trial included 352 patients with major primarily intracranial or GI bleeding who had taken a FXa inhibitor within the last 18 hours. Administration included an intravenous bolus followed by a 2-hour infusion. Andexanet alfa decreased the median anti-FXa activity by 92% for both apixaban and rivaroxaban, with good or excellent hemostasis 12 hours after infusion,[48] although post-infusion drug levels increased to almost half (>75 ng/mL) of the baseline value. At 30-day follow-up, 14% of patients had died and 10% had reported a thrombotic event (mostly patients who did not restart anticoagulation).[48]

Andexanet alfa was approved by the FDA and EMA to treat life-threatening bleeding in patients on apixaban and rivaroxaban.

In patients with rivaroxaban- or apixaban-associated critical site or life-threatening major bleeding, reversal with andexanet alfa is a Class IIa, Level of Evidence B recommendation in the 2019 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation,[46] being also endorse by the European Society of Cardiology and European Heart Rhythm Association.[47] The recommended dose of andexanet alfa depends on the timing of the last apixaban or rivaroxaban dose: last dose >7 hours: iv bolus of 400 mg followed by infusion with 480 mg over 120 minutes; last dose <7 hours: iv bolus of 800 mg, followed by infusion with 960 mg over 120 minutes.

Although the ANNEXA-4 trial included patients receiving edoxaban, the number of patients enrolled was limited,[48] and andexanet alfa is not yet approved for edoxaban-treated patients. However, most recommendations endorse its use for edoxaban reversal.[38]

## Non-specific reversal agents

When specific reversal agents are not available, it is reasonable to use hemostatic agents, such as non-activated prothrombin complex concentrate (PCC) or activated PCC (aPCC). They may counteract DOAC coagulation due to coagulation factor supplementation. Supporting evidence of their use is mostly limited to healthy human volunteers, animal models, *in vitro* studies, and small case series of actively bleeding patients.[49-57] Studies evaluating the effect of hemostatic agents in hemostasis assays showed correction of some coagulation parameters, but results were inconsistent across all DOACs and studies, and correction was not observed for all DOACs.[49,50] Four-factor-PCC (4F-PCC) has been mostly evaluated as a hemostatic agent in FXa inhibitor-treated patients with major bleeding, showing variable improvement in laboratory hemostatic parameters and/or clinical hemostasis.[54-57] The dose normally recommended is 50 U/Kg.

There are no randomized trials investigating the use of aPCC in bleeding patients under DOACs. However, based on the doses used in hemophilia, an initial intravenous dose of 50 U/kg until the maximum dose of 200 U/kg per day is suggested for DOAC-treated patients with major bleeding.[38,47]

According to several guidelines,[38,47] the administration of either 4F-PCC or activated PCC may be considered in patients with life-threatening bleeding if immediate hemostatic support is required and specific reversal agents are not available. Usually, 4F-PCC is preferred to the aPCC (FEIBA) due to its lower potential prothrombotic activity and wider prompt availability.

DOAC anticoagulation reversal strategies will ultimately depend on the resources and experience of each center.

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# 2.3. Heparin

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the most widely used anticoagulants among hospitalized patients worldwide, both presenting bleeding risk.[1,2]

## Unfractionated heparin

UFH is a heterogeneous mixture of different length strands of highly sulfated mucopolysaccharides with different molecular size, anticoagulant activity, and clearance profile. It sticks to endothelial cells, macrophages, and various heparin-binding proteins, leading to unpredictable pharmacokinetics and hence requiring anticoagulant activity monitoring.[2] UFH is also frequently used in the perioperative and intensive care unit settings.

## UFH monitoring

Heparin infusion and dosing may be monitored either through activated partial thromboplastin time (aPTT) or anti-Xa activity.

aPTT is the most widely used laboratory test to monitor heparin. This clotting time depends on several coagulation factors and can be a more accurate measure of patients' coagulation status.[3] However, stable aPTT levels over time are difficult to achieve. The evaluation of heparin anti-Xa level is less dependent on coagulation factors, providing a more accurate measurement of heparin anticoagulant effect and requiring fewer dose adjustments and shorter time to obtain a therapeutic anticoagulant effect.[4] Some guidelines state that either aPTT or heparin anti-Xa level monitoring may be used.

## UFH reversal

When administered intravenously, UFH has a short half-life (between 30 minutes and 2.5 hours, depending on dosage).[2] Therefore, in most cases the use of a reversal agent can be avoided when major bleeding occurs. When UHF anticoagulant effect reversal is required, intravenous protamine sulfate can be administered. Protamine sulfate is a basic protein that binds to the

anionic glycosaminoglycan heparin, rapidly inactivating UFH. One unit of protamine sulfate neutralizes approximately one unit of heparin (or 1 mg of protamine per 100 units of UFH).[2]

The need and dose of protamine sulfate is based on the timing of the last UFH dose. Due to its short half-life, only heparin administered over the past few hours should be considered when calculating the dose of protamine sulfate:[2,5] one unit of protamine sulfate per UFH unit if heparin was stopped within the previous 1 hour or anti-Xa activity is >0.35 U/mL (with a maximum dose of 5000 units or 50 mg); 0.5 units of protamine sulfate per UHF unit if heparin was stopped within the previous 3 hours or anti-Xa activity is >0.1 U/mL.[2,6] Protamine sulfate should not be given if anti-Xa level is ≤0.1 U/mL. aPTT can be used to evaluate UFH neutralization by protamine sulfate.

In emergent cases, 25 mg of diluted protamine sulfate can be administered to patients under continuous UFH infusion, with repeat dosing until a maximum of 50 mg, if needed.[2]

## Low-molecular-weight heparin

LMWH consists of short polysaccharide chains derived from UFH by chemical or enzymatic depolymerization. Several LMWH formulations are available (e.g., enoxaparin, dalteparin, tinzaparin, nadroparin), with different pharmacokinetic properties and anticoagulant activity. LMWH half-lives range from 3 to 6 hours and are dose-independent.[1,2,5] LMWH predominantly presents renal excretion, leading to increased half-life in patients with impaired renal function.[7] It is subcutaneously administered once or twice daily for prophylaxis and treatment of thromboembolism.[1]

## LMWH monitoring

LMWHs have predictable pharmacodynamic profiles and wide therapeutic windows, avoiding routine coagulation monitoring in clinically stable and uncomplicated patients. PT and aPTT have low sensitivity to evaluate LMWH activity. Anti-Xa activity measures LMWH anticoagulant activity and can be used to evaluate and adjust dosing in special patient populations (with impaired renal function, pregnancy, extreme body weight) or when bleeding or thrombotic events occur during LMWH therapy.[2,8,9]

## LMWH reversal

LMWH should be immediately stopped in cases of significant bleeding. Protamine sulfate may be used as a reversal agent for LMWH, but it only partially reverses LMWH anticoagulant activity (due to full reversal of the anti-IIa fraction but only partial reversal of the anti-Xa component – 50–80% reversal action).[2,5,6,10,11] This variability is due to differences in sulfate charge densities between LMWH formulations.

The need and dose of protamine sulfate is based on the timing of the last LMWH dose and on patient's renal function.[2,5] In patients with impaired renal function, LMWH clearance is decreased, and the anticoagulant effect may persist. Guidelines suggest the administration of 1 mg of protamine sulfate per 100 anti-Xa units of LMWH, up to a maximum of 50 mg if LMWH is given within the previous 8 hours or if the anti-Xa activity is >0.5 U/mL.[2] A second dose of 0.5 mg per 100 anti-Xa units can be administered if bleeding persists. If the time since LMWH administration is greater than 8 hours and shorter than 12 hours, or if anti-Xa activity is 0.3–0.5 U/mL, 0.5 mg of protamine sulfate per 100 anti-Xa units should be administered. If more than 12 hours have elapsed since LMWH administration, protamine can be given in patients with impaired renal function with decreased LMWH clearance and ongoing anticoagulant activity.

Protamine sulfate administration may be associated with adverse events, such as hypotension, bradycardia, pulmonary vasoconstriction, allergic reactions, and thromboembolic complications.[2,6,12] Protamine sulfate must be given by slow intravenous infusion at doses ≤5 mg/min to minimize the risk of these events.[2,6]

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# 2.4. Antiplatelet therapy

Antiplatelet therapy (APT) is the gold-standard therapy for secondary prevention of thrombotic events in the context of cardiovascular disorders. With widespread coronary stent implantation, there has been an increased use of more potent antiplatelet drugs to prevent stent occlusion, as single or dual antiplatelet therapy. However, like all antithrombotic drugs, antiplatelets are also associated with an increased risk of bleeding, ranging from minor bruising to severe bleeding, particularly intracranial and gastrointestinal.

## Mechanism of action of antiplatelet drugs

The most frequently used anti-platelet drugs are aspirin, adenosine-diphosphate (ADP)-inhibitors clopidogrel, prasugrel, and ticagrelor, and occasionally glycoprotein (GP) IIb/IIIa inhibitors.

Aspirin irreversibly inhibits cyclo-oxygenase (COX)-1, preventing the production of thromboxane $A_2$ ($TXA_2$) from arachidonic acid, leading to inhibition of $TXA_2$-induced platelet aggregation.[1-3]

ADP receptor (P2Y12) inhibitors prevent ADP-induced platelet activation. Three P2Y12 inhibitors are currently routinely used in the clinics: clopidogrel, prasugrel, and ticagrelor.

Clopidogrel and prasugrel are thyenopyridines, which irreversibly inhibit the P2Y12 receptor for ADP on platelets, preventing ADP binding and platelet aggregation. They must be metabolized to become active.[3,4] Ticagrelor reversibly inhibits the ADP receptor and exhibits rapid effect onset and offset, not requiring metabolic activation.[3,4]

GP IIb-IIIa antagonists inhibit the aggregation of activated platelets. Three agents are approved for clinical use: abciximab, eptifibatide, and tirofiban. Abciximab is a chimeric monoclonal antibody that binds to platelet receptors, whereas tirofiban and eptifibatide are small molecule inhibitors that block the Arg-Gly-Asp (RGD) sequence within GPIIb/IIIa, preventing the association between fibrinogen and von Willebrand factor (vWF).[5,6] These drugs inhibit fibrinogen-mediated platelet binding to allow platelet aggregation. They are all intravenously administered and have short half-lives. GP IIb-IIIa antagonists are likely to be of greatest value when short-term intense antiplatelet therapy is indicated, such as during percutaneous coronary intervention (PCI).[6] Platelet function returns to normal soon after APT infusion has been discontinued.

# Managing gastrointestinal bleeding in patients under antiplatelet therapy

The management of patients on APT presenting with gastrointestinal bleeding (GIB) is controversial. A review of available guidelines regarding APT and GIB showed the absence of clear recommendations on how to manage this clinical situation, besides discontinuing APT.[7,8] However, the duration of action of irreversible oral antiplatelet drugs (e.g., aspirin, clopidogrel, prasugrel) is such that a temporary discontinuation may not have clinical effect for several days and the bleeding event is controlled when it finally does.[1-3] Only ticagrelor presents a shorter half-life (7–9 hours).[4] The risk/benefit balance of stopping these drugs should be weighed, particularly in patients with recent coronary stent placement, as they present a higher risk of stent thrombosis if APT is prematurely discontinued.[9]

Platelet transfusion is unlikely to be beneficial in most GIB cases. A retrospective review reported that it can even be deleterious. Approximately 400 patients on APT and GIB were evaluated, and increased rates of cardiovascular events (23% vs 13%) and significantly increased mortality rates (7% vs 1%) were found in the group of platelet-transfused patients compared to controls.[8] Transfused patients had more severe presentation, but platelet transfusion provided no significant benefit.[8] Recommendations of Gastroenterology societies concerning platelet transfusion differ among them. The American Society of Gastroenterology guidelines include platelet transfusion as an option in severe cases,[6] but the 2018 Asian Pacific Gastroenterology guidelines do not recommend it.[10] Patients who have been under APT represent particular cases regarding platelet concentrate (PC) transfusion and should be the object of an individualized approach based on their general clinical condition.[11]

Even in the setting of intracranial hemorrhage, probably the most severe and life-threatening bleeding scenario, platelet transfusion does not seem to present benefits. The Platelet Transfusions for Intracerebral Hemorrhage (PATCH) trial, performed in patients under APT with spontaneous intracranial hemorrhage, reported that platelet transfusion did not reduce bleeding and was associated with increased mortality and dependence evaluated at three months.[12] Desmopressin, or DDAVP, improves dysfunctional platelet activity by increasing endothelial release of vWF and FVIII levels from endothelial stores.[12] In acquired bleeding disorders, DDAVP has been mainly used as a single intravenous dose of 0.3–0.4 µg/Kg in patients with active bleeding and uremia plus impaired renal function and also in those on APT.[13-15] DDAVP was also evaluated in a meta-analysis of patients on APT or with platelet dysfunction submitted to cardiac surgery.[16] Its use led to a 25% reduction of transfused red blood cells and a 23% reduction of blood loss, with a smaller risk of reoperation due to bleeding. No decrease in mortality or increase in thrombotic events was observed.[16] Overall, very few studies have investigated patients with GIB receiving DDAVP.

An important GIB feature is its association with increased risk of further ischemic events and mortality, which may be related to a prothrombotic state induced by bleeding, but also to APT interruption.[17,18]

Whenever possible, early endoscopic bleeding control should be performed, as this procedure improves outcomes.[19] Proton pump inhibition (PPI) is also recommended in all patients without contraindications, as it has been shown to benefit those under single- and dual-agent APT, both in the acute bleeding[19] and bleeding recurrence prevention[20,21] settings.

When APT is discontinued, the need and timing of reintroduction should be discussed. The reason why patients are taking antiplatelet medications should be reviewed. When endoscopic control is achieved, and the recurrent bleeding risk is low, APT may be safely continued throughout. For patients with high risk of bleeding recurrence on single-agent therapy, the antiplatelet drug may be suspended for 3–7 days. For patients on dual APT, particularly following recent cardiac stent insertion, aspirin should be continued, and a second agent reintroduced as soon as possible.[21]

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# 2.5. Restarting anticoagulation after gastrointestinal bleeding

Antithrombotic therapy is often stopped following gastrointestinal bleeding (GIB).[1,2] However, most patients benefit from antithrombotic resumption, which is associated with improved survival and reduced incidence of thrombotic complications, providing net clinical benefit.[3,4]

In a systematic review of 12 observational studies including 3,098 patients, those with oral anticoagulant (OAC)-associated GIB who resumed anticoagulation had a lower risk of thromboembolism and death compared to those who did not but presented an increased risk of recurrent bleeding.[5] In three other studies comparing patients who did and did not resume anticoagulants after GIB, the first experienced a reduction in thromboembolic events, reduced mortality rate, and no rebleeding increase.[6-8]

It is important to evaluate individual patients' thrombotic and bleeding risk to make decisions regarding antithrombotic therapy after bleeding events.[1,2]

The indication for antithrombotic therapy must be reassessed to determine whether it is recommended according to clinical guidelines.[1] Patients with mechanical valve prosthesis, atrial fibrillation (AF) with a $CHA_2DS_2VASc$ score ≥4, valvular AF, venous thromboembolism (VTE) within 3 months, unprovoked, recurrent VT, and cancer-associated VTE present high thrombotic risk[9-12] and benefit from restarting anticoagulation, even if the rebleeding risk is high.

After a bleeding event, it is crucial to assess the bleeding risk using bleeding scores. These scores include non-modifiable, potentially modifiable, and modifiable risk factors.[9,13] Whenever possible, modifiable and potentially modifiable risk factors should be corrected prior to resuming antithrombotic therapy, namely hypertension, labile international normalized ratio (INR) in patients on vitamin K antagonists (VKAs), impaired renal function, alcohol intake, anemia, thrombocytopenia, and significant drug interactions potentially increasing OAC levels. It is very important to choose the most suitable and correct OAC dosing according to patients' characteristics (age, weight, renal and hepatic function, drug interactions) and indication for anticoagulation.

Characteristics of the bleeding event influence the risks associated with restarting antithrombotic therapy, namely bleeding location, whether the bleeding cause was identified and treated, and whether further surgical or procedural interventions are planned.[1,2]

Bleeding risk is dynamic, and evaluation of bleeding risk factors should be made at every patient contact,[14] towards improved efficacy and safety of antithrombotic therapy.

# Timing of anticoagulation restart

The optimal timing for resuming OACs must be decided according to the need to prevent thrombotic events while minimizing rebleeding. GI practice guidelines suggest resuming anticoagulation as soon as the risk of cardiovascular complications outweighs the risk of bleeding.[1,2]

Patients must be included in this decision and explained the risks of withholding anticoagulation and the signs of rebleeding.

Patients with high thrombotic risk should initiate anticoagulation once they are clinically stable and hemostasis is achieved. For patients with high rebleeding and thrombotic risk, intravenous unfractionated heparin is recommended due to its short half-life and availability of a reversal agent (protamine sulfate), until bleeding risk decreases and OAC can be restarted. If a relative or absolute contraindication exists to restart anticoagulation, nonpharmacological therapies should be considered.

For most patients with high bleeding risk and low/moderate thrombotic risk, prophylactic doses of parenteral anticoagulants (subcutaneous low-molecular-weight heparin) can be administered. Temporary interruption of anticoagulation for a short period of time is also acceptable for most patients with low thrombotic risk. If rebleeding occurs, further interruption of anticoagulant therapy will increase the thrombotic risk.

Evidence about the timing of OAC resumption is limited. In one study, anticoagulation was restarted at the time of discharge (median length of stay of 5 days) and fewer thromboembolic events were noted at 90 days, with a greater rate of bleeding events.[7] Another study compared the outcomes of 653 patients according to different timings of OAC restart. Patients restarting warfarin >7 days after a bleeding event showed improved survival and lower rates of thromboembolic events, without increased risk of GIB recurrence.[15] Based on these results, OACs should be resumed between 7 and 30 days after the bleeding event, specifically in the second week for most patients.

When restarting OACs, it is important to consider switching to an alternate agent.[1,9] If a patient under VKAs presents a bleeding event associated with supratherapeutic international normalized ratio (INR), switching to a direct oral anticoagulant (DOAC) should be considered. A decrease in renal function may increase DOAC drug levels and switching from a DOAC to a VKA may be mandatory. Switching between DOACs can also be important. After results from clinical trials and real-world studies, the 2020 European Society of Cardiology (ESC) guidelines recommended apixaban or dabigatran at a dose of 110 mg twice daily in patients with previous GIB, as these agents are associated with lower GIB risk compared with warfarin.[9,16-18]

Resuming anticoagulation in patients with cancer is particularly challenging, as they present both a high risk of bleeding and thrombosis associated with the disease itself and

cancer-associated treatments. A multidisciplinary team approach is desirable, balancing the decrease in thrombotic risk with the risk of serious bleeding, which depends on cancer type, site, staging, and anti-cancer therapy.[19]

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# 3. Cardiovascular disease/ Coronary stent

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## 3.1. Introduction

Patients submitted to myocardial revascularization with stent present a high risk of stent thrombosis and major adverse cardiac events (MACE; Table 1) and double antiplatelet therapy is therefore recommended to minimize their incidence.[1]

**Table 1. Predictive factors of MACE in patients with coronary stent – High cardiovascular risk patients**

| |
|---|
| **Clinical** |
| • Revised cardiac risk index >2 |
| • Emergent/urgent surgery |
| • Any stent <4-6 weeks after ACS (especially if biomarkers +) |
| • DES <8-12 weeks and SHID |
| • Premature discontinuation of platelet antiaggregation |
| • HTPR |
| • Major perioperative bleeding |
| **Related to the procedure** |
| • Incomplete revascularization after PCI |
| • Persistent myocardial ischemia after PCI |
| • Ostial, calcified, long and short lesions |

ACS, acute coronary syndrome; DES, drug-eluting stent; HTPR, high on-treatment platelet reactivity; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease

Gastrointestinal hemorrhage is the most frequent complication in patients medicated with antithrombotic agents (antiplatelet or anticoagulant agents).[2]

Major hemorrhage is associated with a significant increase in the risk of death, myocardial infarction, and stroke.[3] Discontinuation of antithrombotic drugs may lead to an increased rate of thrombotic events due to progressive recovery of platelet function and coagulation activity. In addition, bleeding may elicit prothrombotic responses beyond those related to discontinuation of antithrombotic drugs.[4]

# 3.2. Types of stents

A stent is a rigid structure that prevents constriction-mediated or elastic retraction-mediated vessel lumen occlusion.[1, 5]

Two types of stents are currently available: bare metal stents (BMS) and drug-eluting stents (DES), which include bioresorbable stents (BRS):[1,5-7]

- BMS – Mesh-like tubes of thin wire with no pharmacological coating. The advantage of BMS is providing full endothelial coating in approximately 12 weeks, with a reduction in the risk of stent thrombosis. They are however associated with a higher risk of restenosis by tunica intima proliferation (2-30%).[1,6]

- DES – Metallic structure with a polymer coating loaded with an antiproliferative agent (ex. paclitaxel, sirolimus, or derivatives). This drug is released in a gradual and controlled manner (i.e., by elution), enabling local diffusion in vascular tissues and preventing excessive vascular growth (neointimal hyperplasia) and vascular occlusion. Second- and third generation DES have a thin cobalt or platinum chromium structure coated with polymers that reduce local inflammation and interference in the reendothelialization process.[1,5,6]

The combined treatment of aspirin and a P2Y12 inhibitor is effective, although the risk of late and very late thrombosis has considerably declined since the introduction of newer DES. Most potent P2Y12 inhibitors are preferred over clopidogrel, which further increases the risk of hemorrage.[8]

Other comorbidities, such as atrial fibrillation and/or previous thromboembolism, require combined antiplatelet-anticoagulant therapy, which significantly increases the risk of hemorrhage.

# 3.3. Thrombotic risk assessment

An accurate medical history is crucial to assess thrombotic risk, which depends on:

a) The clinical context that determined stent placement.
b) The type of stent.
c) The duration of dual antiplatelet therapy.[9,10]

# 3.4. Management of gastrointestinal hemorrhage in patients on dual antiplatelet therapy

The decision to discontinue or maintain dual antiplatelet therapy (DAPT) depends on the likelihood of myocardial ischemia (indication for DAPT, period between stent placement and hemorrhage) versus the risk of prolonged/recurrent hemorrhage. Therefore:

1) Consulting with the specialty that prescribed antiplatelet therapy is recommended before discontinuing antiplatelet agents in cases of significant gastrointestinal (GI) hemorrhage.[4,11]

2) The decision to discontinue both antiplatelet agents, particularly if the stent has been recently placed (**Table 2**),[7,9,10,12] should only be taken if there is massive, life-threatening hemorrhage and its source cannot be treated. In this rare scenario, the patient should be transferred to a hospital with an Interventional Cardiology Unit available.[13]

**Table 2. Minimum duration of dual antiplatelet therapy before noncardiac surgery**

- BMS: Stable CAD and low risk: >6 weeks
- DES: Stable CAD and low risk: >8 weeks to <6 months
- BMS or DES: ACS, PCI complex or high thrombotic risk: >6-12 months
- BRS: 12 months

ACS, acute coronary syndrome; BMS, bare metal stent; BRS, bioresorbable stent; CAD, coronary artery disease; DES, drug-eluting stent; PCI, percutaneous coronary intervention

## Summary of guidelines on antiplatelet therapy after hemorrhage:[4,11]

**1-** High or very high thrombotic risk and minor or major hemorrhage:

a) Maintain low-dose aspirin;

b) Restart second antiplatelet agent as soon as possible once the hemorrhage has been controlled. A case-by-case approach weighing all risks involved is recommended.

**2-** Intermediate thrombotic risk and minor or major hemorrhage:

a) Stop DAPT;

b) Restart aspirin as soon as the hemorrhage has been controlled, preferably within 3 days;

c) Restart a second antiplatelet agent if the thrombotic risk outweighs the bleeding risk;

d) If a new-generation DES has been in place for under three months, restart DAPT until a three month period as been acomplished;

e) If a new-generation DES has been in place for over three months and there is risk of recurrent hemorrhage, only one antiplatelet agent is recommended (aspirin or clopidogrel).

f) Although less effective, clopidogrel has a lower bleeding risk and may be the IP2Y12 of choice after hemorrhage due to prasugrel or ticagrelor. The duration of action of prasugrel (7 to 10 days) or ticagrelor (3 to 5 days) should be considered when restarting an IP2Y12.

g) The addition of a proton pump inhibitor (PPI) is recommended in all cases of upper GI hemorrhage. Although there are no reports of pharmacological interactions between PPIs (mainly omeprazole) and clopidogrel leading to poor outcomes, the use of PPIs less extensively metabolized by CYP2C19 (pantoprazole) is advisable.[11]

# 3.5. Limitations of current guidelines

Although some guidelines are in place for the treatment and management of patients with stents, their main variables are time of elective surgery and management of antithrombotic therapy according to the type of stent. In addition, as guidelines are based on low-quality evidence and experts' opinion, most of their recommendations are frequently different. Finally, recommendations apply to the first 12 months after percutaneous coronary intervention (PCI) only.[1]

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## COMORBIDITIES

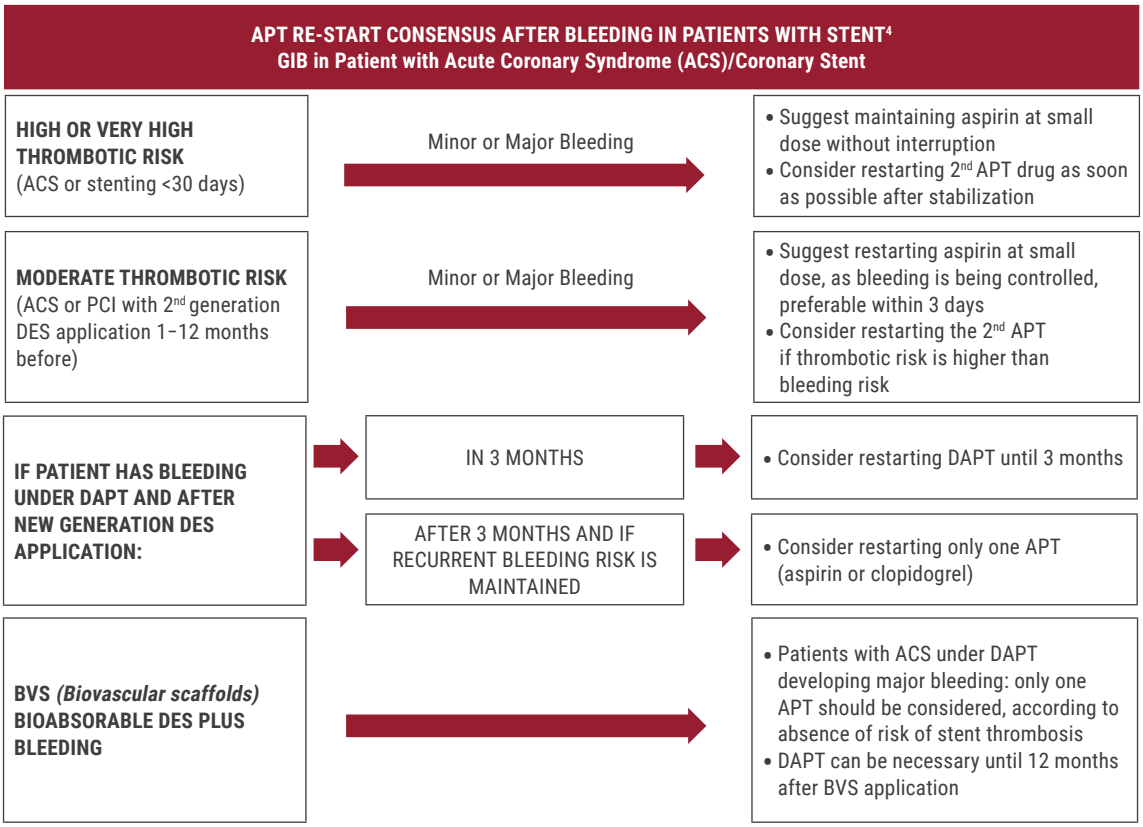
| | | |
|---|---|---|
| Liver cirrhosis/portal hypertension (PHT) | If liver cirrhosis/ PHT (suspected or confirmed): Consider specific therapy before endoscopic confirmation. | • Start immediately vasopressors (terlipressin/octreotide/ somatostatin), if not contraindicated<br>• Start prophylactic antibiotic<br>• Monitoring: MELD, Child-Pugh, in pre-transplant evaluation? Status on list?<br>• Collect blood + urine + ascites for bacteriological tests<br>• Consider prophylaxis for hepatic encephalopathy<br>• Consider Sengstaken-Blakemore balloon if clinical situation is not controlled (alg. 3.1.1.) |
| Chronic renal disease | • Anemia<br>• Platelet dysfunction<br>• Thrombocytopenia | • Dialysis without heparin<br>• Correct anemia: ideally HTC: 30% (Grade 1C)[14]<br>• Fibrinogen concentrate: 25–50 mg/Kg[15,16] (2–4 g) iv<br>• Desmopressin: 0.3 mcg/kg iv[14] |
| Ischemic coronary disease | • Maintain Hg ≥8 – ≥9 g/dL[15-17]<br>• Proceed according to ongoing therapy – mostly with APT<br>• Majority submitted to b-blockers – interferes with Shock Index<br>• See drugs (oral anticoagulants, heparin, APT) and stents | |

## ANTICOAGULATION MANAGEMENT IN GIB

| | | | |
|---|---|---|---|
| VKA (po)[18,19]<br>Evaluate INR - INR >2<br>(Do not delay endoscopy if INR <2.5)[20] | • Discontinue VKA<br>• Vitamin K – 5–10 mg iv<br>• PCC – 15–30 IU/Kg iv | | |
| **DOAC (po)**[18,21,22]<br>• Evaluate type, dose, time from last intake<br>• Evaluate coagulation, renal clearance | • Discontinue DOAC<br>• Last intake < 2–4 h: oral charcoal<br>• Dialysis: Dabigatran | **Dabigatran**<br>• Idarucizumab: 2 x 2.5 g iv | **FXa Inhibitors**<br>• PCC – 25–50 IU/Kg iv |
| **HEPARIN (iv)** [18]<br>• Consider UFH or LMWH | **UFH**<br>• Discontinue perfusion<br>• Protamine sulphate 1 mg/100 IU heparin | **LMWH**<br>• Discontinue perfusion<br>• Protamine sulphate 1 mg/1 mg enoxaparin | |

## ANTIPLATELET MANAGEMENT IN GIB

| | | |
|---|---|---|
| **Antiplatelet Therapy (APT)**[21]<br>• Aspirin or<br>• Thienopyridines or<br>• Double therapy (DAPT) | **Acetylsalicylic acid**<br>(Aspirin)<br>Do not discontinue<br>(Discuss with cardiologist) | **Thienopyrides**<br>• Discontinue + Platelet concentrate (PC)*<br>(1 pool of PC or 1 platelet apheresis unit/60–70 Kg)<br>• If severe GIB (individualized approach);<br>*Actually this matter is not consensual[23] (previous TM specialist opinion) |




- APT (single or double) may be continued without interruption if low risk bleeding stigmas are identified in upper endoscopy[13]
- Association of PPI to DAPT is recommended in all GIB cases[13]
- Also consider gastroenterological guidelines about this subject[13]

ACS, acute coronary syndrome; alg, algorithm; APT, antiplatelet therapy; DAPT, double antiplatelet therapy; DES, drug-eluting stent; DOAC, direct oral anticoagulant; GIB, gastrointestinal bleeding; Hb, hemoglobin; Htc, hematocrit; INR, international normalized ratio; iv, intravenous; LMWH, low-molecular-weight heparin; MELD, model for end-stage liver disease; PC, platelet concentrate; PCC, prothrombin complex concentrate; PCI, percutaneous coronary intervention; PHT, portal hypertension; PPI, pump proton inhibitor; po, per os; TM, transfusion medicine; UFH, unfractionated heparin; VKA, vitamin K antagonist

**Algorithm 2.** Potentially aggravating factors in gastrointestinal bleeding

# Gastrointestinal Bleeding

## Introduction

**Nuno Almeida, Cilénia Baldaia**

Gastrointestinal bleeding (GIB), or GI hemorrhage, is responsible for 350 hospitalizations/100,000 individuals annually in the United States.[1] According to Ell C *et al*., GIB can be divided in three types: upper (UGIB), middle (MGIB), and lower (LGIB).[2] In the first epidemiological studies, UGIB was clearly the most common, but GIB epidemiology has changed in the last decades, largely due to a decrease in the prevalence of UGIB.[3,4] UGIB represents approximately 50% of all GIB admissions, followed by LGIB with 40% of cases and MGIB with 10%. Globally, LGIB seems to have a more benign course than UGIB, but several studies are now challenging this perception.[4] In fact, there is a global lack of high-quality epidemiological studies focusing GIB, particularly LGIB.[4]

UGIB incidence is decreasing due to *Helicobacter pylori* (*H. pylori*) eradication, increasing use of proton pump inhibitors (PPIs), ease of access to endoscopy, and increased efficacy of endoscopic hemostatic techniques.[4] On the contrary, the incidence of complications in the lower GI tract is increasing.[6] For example, bleeding from colonic diverticular disease has increased from 3.3 to 8/100,000 person years.[7]

GIB is a common medical emergency worldwide, with a mortality rate of 7% at hospital admission that increases to 26% if bleeding occurs during hospitalization for other causes.[8] Optimized management of comorbidities has an impact on clinical outcomes, and a multidisciplinary coordination between Gastroenterology, Surgery, Anesthesiology, Transfusion Medicine, Intervention Imaging, and Intensive Medicine is of great value.[9]

Studies comparing patients with different types of bleeding show that those with LGIB historically tend to be older and have more comorbidities than patients with UGIB.[4,10,11] No differences in antiplatelet and oral anticoagulation use have been reported between both groups.[10,11]

Clinically, GIB can be overt, when there are visible signs of blood loss from the digestive system, or occult, when there is iron-deficient anemia and/or positive fecal occult blood without visible bleeding. The term 'obscure' is applied in the few cases in which the hemorrhage source is not identified after a thorough and complete gastrointestinal tract examination (including the small bowel).[12]

Overt GIB can present as hematemesis, melena, or hematochezia. Hematemesis is defined as vomiting of blood and can be bright red, suggesting ongoing bleeding, or dark, corresponding to digested blood. Melena is defined as black tarry stools, and hematochezia as bright red blood

per rectum. Hematemesis is a synonym of UGIB. Melena can occur in cases of bleeding from the upper GI tract, small bowel, or proximal colon. Hematochezia is usually a LGIB manifestation but can also be present in cases of upper or mid GIB with significant blood loss.

The initial approach to the patient presenting with GIB includes clinical evaluation and simultaneous hemodynamic and cardiorespiratory stabilization.[13,14]

It is important to recognize signs of liver disease and other comorbidities and identify patient's medications, including oral anticoagulants, antiplatelet therapy, and nonsteroidal anti-inflammatory drugs. Previous abdominal or vascular surgeries, such as abdominal aortic repair, are also important for the differential diagnosis. Vital signs must be monitored according to clinical severity, speed of evolution, and hospitalization level. It is difficult to quantify blood loss in GIB. In an early phase, normal hemoglobin and blood pressure do not exclude significant hemorrhage. At this stage, tachycardia is the best early sign of severity, except if patients are under β-blocker therapy.[13,14]

GIB is a medical emergency with non-negligible mortality rate. In UGIB, for instance, the 30-day mortality rate remains at 11%.[15] It is therefore important to implement protocols and algorithms that can be easily followed by medical professionals managing patients with GIB.[9]

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# Upper gastrointestinal bleeding

## Cilénia Baldaia

In the classical definition of gastrointestinal bleeding (GIB), the duodenojejunal (DJ) junction with the ligament of Treitz differentiate upper and lower GI tract. Due to de expansion of enteroscopy and capsule endoscopy, nowadays the landmark is the ampulla of Vater. Bleeding above it considered upper GI bleeding, and below is termed lower GI bleeding. Upper GIB (UGIB) is a common problem. It commonly presents with hematemesis (vomiting of blood or coffee ground-like material) and/or melena (black, tarry stools). In 5–10% of patients with severe UGIB, hematochezia is the cardinal symptom.

Factors predictive of UGIB include patient-reported history of melena, melenic stool on examination, blood or coffee grounds in nasogastric lavage, and a blood urea nitrogen (BUN) to serum creatinine ratio greater than 30.[1]

Use of a nasogastric tube in cases of acute UGIB (AUGIB) suspicion is not recommended, as no benefits in clinical outcomes have been demonstrated.

AUGIB is a frequent medical emergency. It can be classified as variceal/portal hypertension-related or non-variceal, the latter being more frequent.

UGIB is more frequent in men than in women and in older ages, and its hospitalization rate is approximately sixfold higher than lower GIB (LGIB).[2]

Upper gastrointestinal (GI) endoscopy and modern endoscopic treatments can control most cases, but it should be noted that the source of bleeding is not identified in as much as 15% of patients. It is important to exclude conditions with bleeding sources outside the GI tract when performing the medical history, such as epistaxis and hemoptysis.

The most common causes of non-variceal UGIB are peptic ulcers, erosive gastritis, and erosive esophagitis. Other causes, such as neoplasia, aortoenteric fistula, angiodysplasia, hemobilia, and hemosuccus pancreaticus, can be suspected through clinical clues in the initial assessment. Concomitant symptoms, medications, and comorbidities can suggest specific causes.

After effective medical and endoscopic treatment, both short- and long-term prognosis are favorable for peptic ulcer bleeding. Despite these advances, the mortality rate associated with this condition has not improved in the last decade, with 30-day mortality rates ranging from 5% to 12% globally. [3]

Data from 2007 in the UK reported a mortality rate of 10% for nonvariceal UGIB, rising to 26% in inpatient bleeds.[4]

Moreover, after surviving a bleeding episode, patients may be at risk of increased long-term mortality from reasons other than peptic ulcer bleeding. This may be related with underlying comorbid conditions rather than with the bleeding *per se*. Bleeding may be an indicator of deterioration or undiagnosed coexisting comorbidities. Clinicians should take a global approach and be vigilant of concomitant non-GI diseases beyond the bleeding episode. [3]

A multidisciplinary approach is required for optimal management of these patients. Pre-, peri-, and post-endoscopy management is of outmost importance, as management of comorbidities *ad initium* can impact outcomes.

The authors suggest two distinct algorithms in the approach to nonvariceal and variceal UGIB in the pre-, peri-, and post-upper GI endoscopy setting, to identify lesion location and type, assess endoscopy timing using severity scores, identify risk factors for rebleeding, and implement effective hemostatic endoscopic procedures, if feasible.

# Upper gastrointestinal bleeding associated with portal hypertension

UGIB related to portal hypertension has specific management and prognosis. The most frequent cause of portal hypertension is liver cirrhosis.

In patients with cirrhosis, varices form at a rate of 5–15% per year, and one third of patients with varices develop variceal hemorrhage.[5] It is a medical emergency frequently requiring intensive care admission.

Variceal bleeding is a dreaded decompensation in cirrhosis, with distinct mortality whether it is an isolated cirrhosis complication (5-year mortality rate ≈ 20%) or associated with other complications (5-year mortality rate >80%). Therefore, it is important to consider the cirrhosis stage, liver function score (Model For End-Stage Liver Disease [MELD] score), and presence of other (concomitant or previous) cirrhosis complications. The immediate treatment goals in these patients are bleeding control and prevention of early recurrence (within 5 days) and 6-week mortality.[6]

Besides the general and initial patient approach (previously described in this book), specific attitudes are of utmost importance in cases of suspicion of AUGIB related to portal hypertension. Data shows that the use of vasoactive agents is associated with lower 7-day all-cause mortality and transfusion requirements.[7] Therefore, it is crucial to start vasoactive drugs as soon as possible, even before diagnostic endoscopy, to confirm portal hypertension-related lesions. All vasoactive drugs used in the control of acute hemorrhage consist of intravenous infusions.

In the initial assessment, past medical history and laboratory data are important to determine cirrhosis stage and liver dysfunction through scores as MELD, Child-Pugh, and Acute-on-Chronic Liver Failure (ACLF), which correlate with overall mortality. Rates of infection and death are low in Child-Pugh class A patients with cirrhosis and GI hemorrhage.

Patients with cirrhosis and variceal/nonvariceal GI hemorrhage are at high risk (≈20%) of bacterial infections, which are associated with recurrent hemorrhage and death. Antibiotic prophylaxis should be started as soon as possible (short-term duration, maximum 7 days). Blood and urine cultures should always be performed, as well as ascitic fluid culture, if present. Importantly, the use of broad-spectrum antibiotics is associated with multi-resistant infections.

Intravenous ceftriaxone has been shown to be more effective in preventing infections than oral norfloxacin. The choice of the specific antibiotic should be based on patients' individual risk features and local antimicrobial susceptibility. A prophylactic dose of ceftriaxone (1 g/24 hours) is the first choice in patients with advanced cirrhosis or on quinolone prophylaxis, and in areas with high prevalence of quinolone resistance, as in Portugal.[8]

Upper GI endoscopy should be performed until 12 hours after admission. In cases of persistent bleeding and hemodynamic instability, endoscopy should be performed earlier. For variceal bleeding, the most common endoscopic treatment is rubber band ligation. In cases of massive bleeding, placement of a Sengstaken-Blakmore or self-expandable covered stent (ELLA stent) can be lifesaving and gives time to implement an effective endoscopic treatment or transjugular intrahepatic portosystemic shunt (TIPS). Endoscopic application of hemostatic nanopowder is another alternative as bridge therapy if hemorrhage control is not successful.

The use of lactulose or lactitol as soon as oral or enteric route is available after bleeding control prevents another complication: encephalopathy.

As soon as acute bleeding is controlled, secondary prophylaxis of variceal bleeding should be planned and implemented, usually using non-selective beta blockers, as carvedilol, and programmed band ligation. Outpatient follow-up in Hepatology is recommended.

## Non-variceal upper gastrointestinal bleeding

Besides global assessment, specific attitudes are required in cases of non-variceal UGIB. The most used risk scores for this condition are Rockall score and Glasgow Blatchford score (GBS). Rockall is the preferred score for assessing mortality risk, and GBS for assessing the need for endoscopic therapeutic intervention, being used in pre-endoscopy risk stratification. GBS components include BUN, hemoglobin, systolic blood pressure, pulse, and presence of melena, syncope, hepatic disease, and/or cardiac failure, and ranges from zero to 23. The higher this

score, the higher the probability of the patient requiring endoscopic intervention. A simplified GBS has been developed, with an accuracy for endoscopic intervention similar to GBS and better than Rockall score.[9]

GBS has a high negative predictive value, correctly identifying 98% (95% CI 89–100 %) of patients not requiring any subsequent intervention.[10] It uses simple laboratory and bedside data without the need for endoscopy data.

Patients with scores of 0-1 can be treated as outpatients if diagnosis and treatment in due time is feasible. These patients should be informed of risk signs and maintain contact with the discharging hospital. Reference to a general practitioner or cardiologist to urgently assess the risks of temporarily withholding anticoagulants is advisable until lesion diagnosis is established and rebleeding risk assessed.[11]

Patients with GBS >1 should start intravenous proton pump inhibitors (PPIs) as bolus followed by continuous infusion (80 mg followed by 8 mg/hour) as soon as possible, but this should not delay endoscopy. Importantly, acid suppression with H2 receptor antagonists has not been shown to significantly lower the rate of ulcer rebleeding.[9]

Nasogastric or orogastric aspiration/lavage is not mandatory, but intravenous erythromycin 30-120 minutes before endoscopy improves endoscopic visualization, particularly in presence of signs of active bleeding, as ongoing hematemesis and/or hemodynamic instability. QTc-interval monitoring should be conducted. Metoclopramide can be used as an alternative drug.

Following hemodynamic resuscitation, upper GI endoscopy should be early performed (≤24 hours) in inpatients. Although guidelines do not recommend very early (<12 hours) upper GI endoscopy, it should be considered in cases of patients with persistent hemodynamic instability (tachycardia, hypotension) despite volume resuscitation, in-hospital bloody emesis/nasogastric aspirate, or contraindication to interrupt anticoagulation.

Endoscopy allows to determine the lesion's location, type, and rebleeding risk and perform endoscopic hemostasis according to that information.

In patients with peptic ulcers, the most frequent type of lesion, hemostasis is performed in cases of spurting or oozing bleeding (Forrest classification Ia and Ib, respectively) or nonbleeding visible vessels (Forrest classification IIa), as these lesions have increased risk. For lesions with an adherent clot (Forrest classification IIb), careful endoscopic clot removal can be performed. Once the clot is removed, any underlying active bleeding or nonbleeding visible vessel should receive endoscopic hemostasis. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines suggest that endoscopic hemostasis using a cap-mounted clip should be considered as first-line therapy in selected actively bleeding ulcers (Forrest classification Ia, Ib) – specifically those with >2 cm in size, with a large visible vessel with >2 mm, or located in a high-risk vascular area (e.g., gastroduodenal, left gastric arteries) – and

in excavated/fibrotic ulcers.[6] Peptic ulcers with a flat pigmented spot (Forrest classification IIc) or clean base (Forrest classification III) do not require endoscopic hemostasis.

PPI therapy is indicated for patients receiving endoscopic hemostasis and with adherent clots not receiving endoscopic hemostasis and should be administered at high dose as an intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour) for 72 hours postendoscopy.

Factors associated with rebleeding include hemodynamic instability (systolic blood pressure <100 mmHg, heart rate >100 beats per minute), hemoglobin <10 g/L, active bleeding at the time of endoscopy, large ulcer size (>1–3 cm, according to various studies), and ulcer location (posterior duodenal bulb or high lesser gastric curvature).[12]

Guidelines do not recommend routine second-look endoscopy as part of non-variceal UGIB management. However, in cases of clinical evidence of rebleeding following a negative initial upper endoscopy or after successful initial endoscopic hemostasis, a second upper endoscopy with hemostasis if indicated. In case of failure of this second hemostasis attempt, transcatheter angiographic embolization or surgery should be considered.

If upper endoscopy is not conclusive regarding the level and/or cause of AUGIB, clinicians should consider other tests, including CT angiography and angiography in cases of active bleeding, deep small bowel enteroscopy, and (rarely) intraoperative enteroscopy. Barium studies are contraindicated for this purpose, as barium interferes with subsequent endoscopy, angiography, or surgery.

*Helicobacter pylori* infection status should be assessed in patients with peptic ulcer bleeding. If it is negative in acute setting, retesting should be performed, as it can be a false negative. *H. pylori* should be eradicated, and therapeutic success should be documented afterwards.

For patients treated with low-dose aspirin for secondary cardiovascular prophylaxis who develop peptic ulcer bleeding, aspirin should be resumed immediately following index endoscopy if the risk of rebleeding is low (Forrest classification IIc-III). In patients with high-risk peptic ulcer (Forrest classification Ia, Ib, IIa, IIb), early aspirin reintroduction is recommended by day 3 after index endoscopy, provided that adequate hemostasis has been established. Management of anticoagulation/antiaggregation is a balance between hemorrhage risk and thrombotic risk and can be complex, as described in **Chapter 2.**

## Acknowledgments

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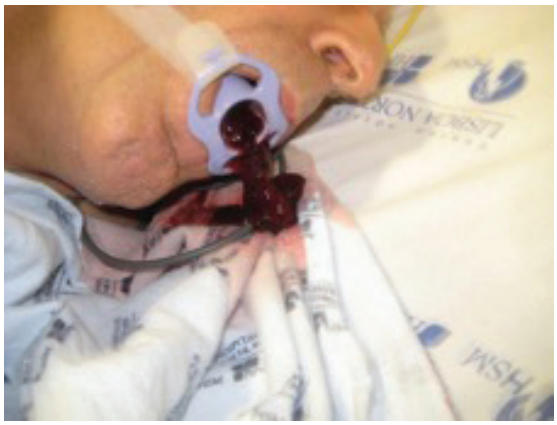


**Figure 1.** Hematemesis

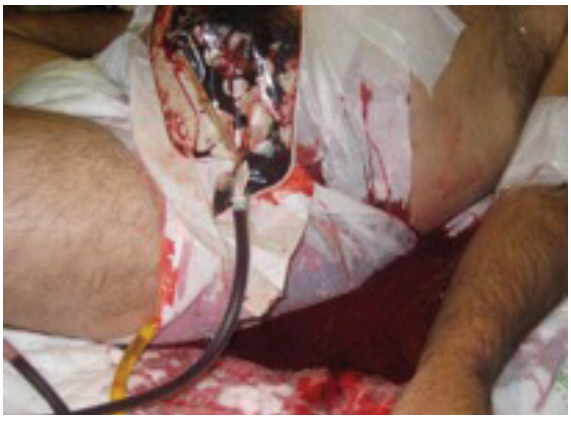


**Figure 2.** Hematochezia

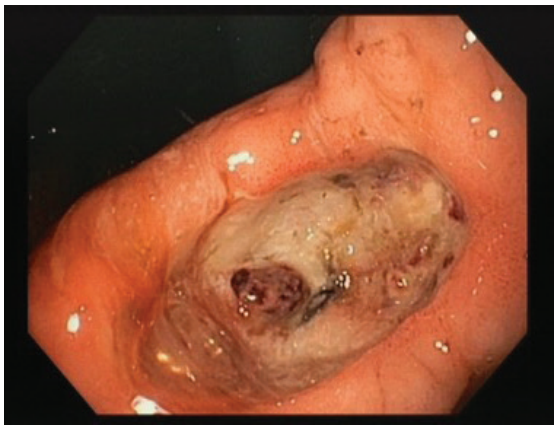


**Figure 3.** Notch ulcer Forrest IIa

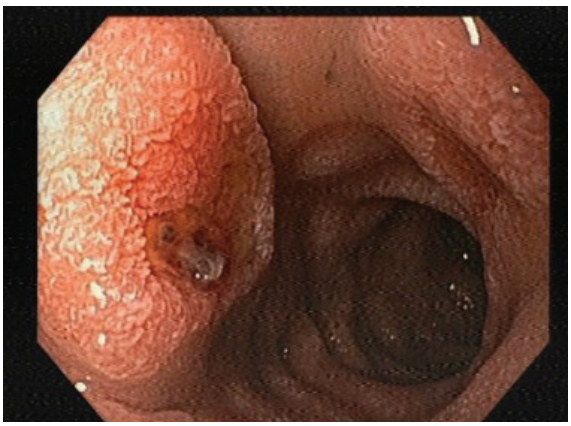


**Figure 4.** Bulbar ulcer Forrest IIa

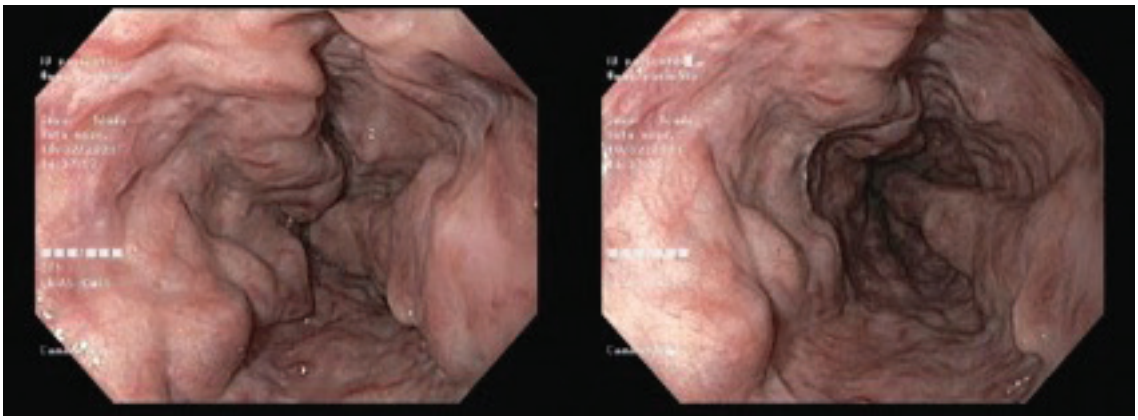


**Figure 5. Large esophageal varices**

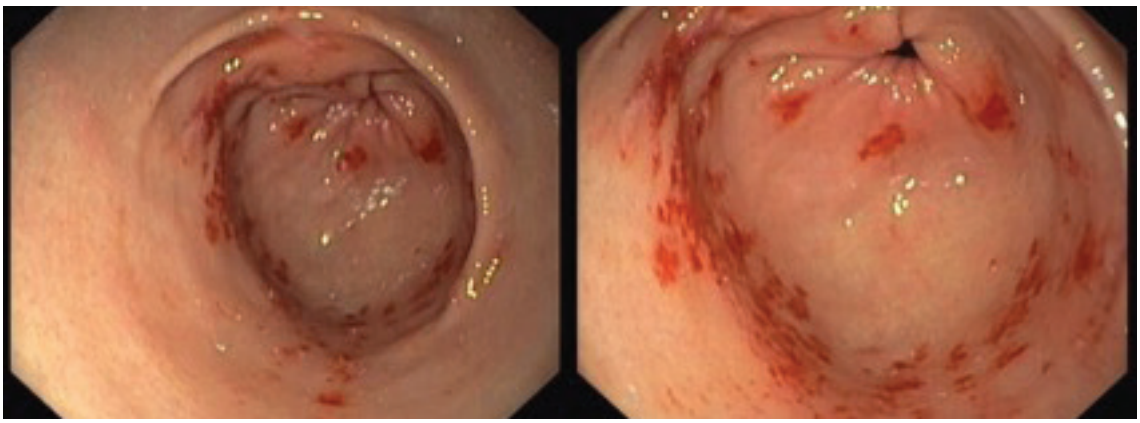


**Figure 6.** Antrum vascular ectasias

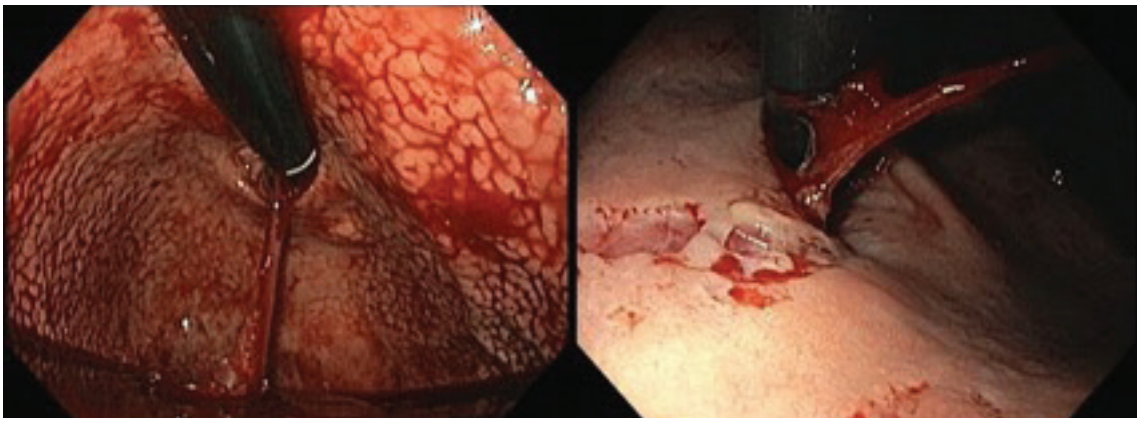


**Figure 7.** Mallory-Weiss laceration

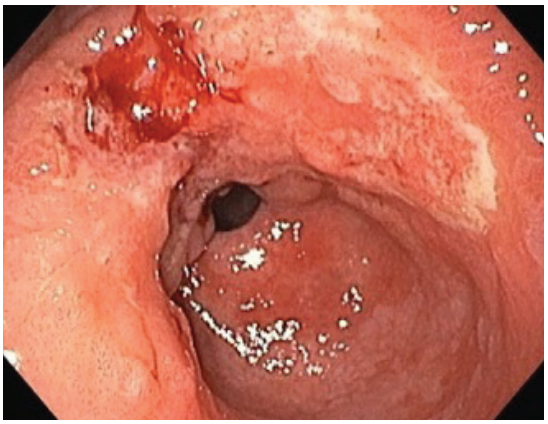


**Figure 8.** Gastric antrum neoplasm

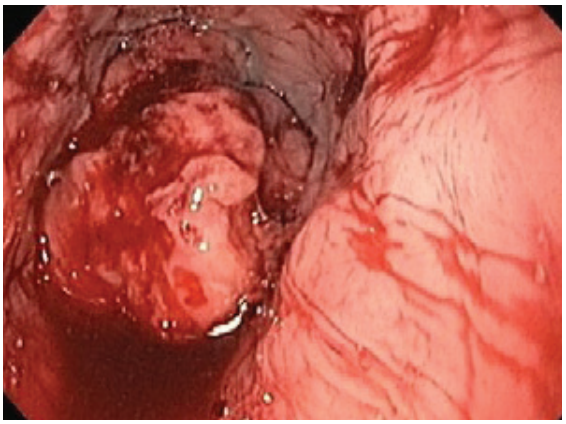


**Figure 9.** Neoplasm of the middle esophagus

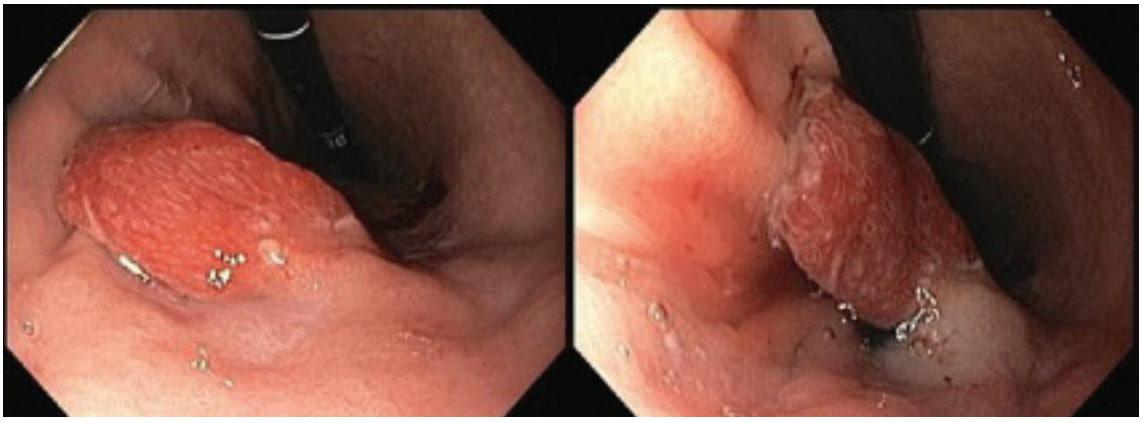


**Figure 10.** Pediculated gastric polyp with erosions

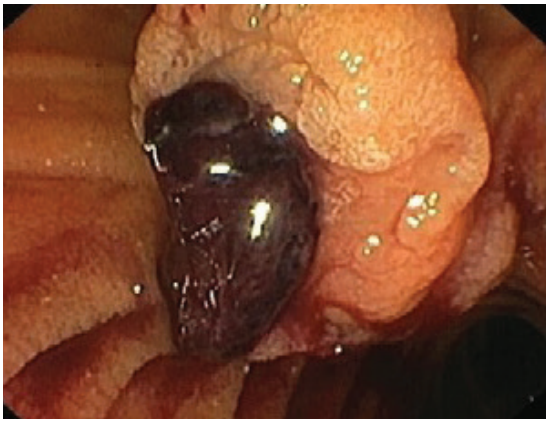


**Figure 11.** Hemobilia

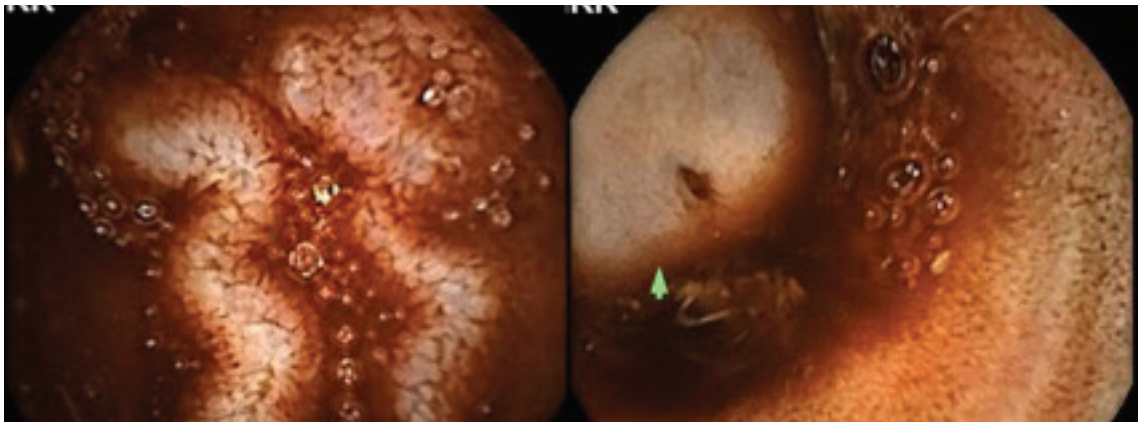


**Figure 12.** Ectopic varices of the jejunum and point of rupture

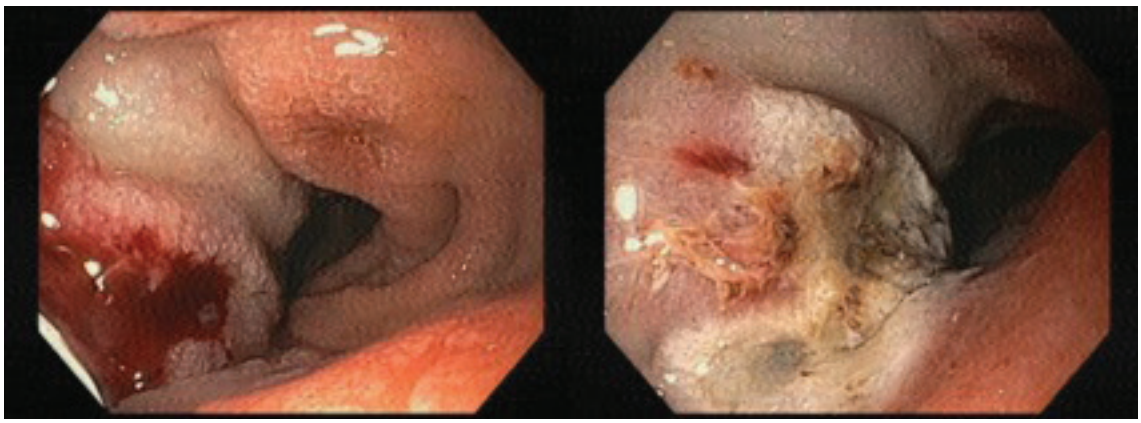


**Figure 13.** Duodenal ulcer Forrest Ib before and after hemostasis with BICAP

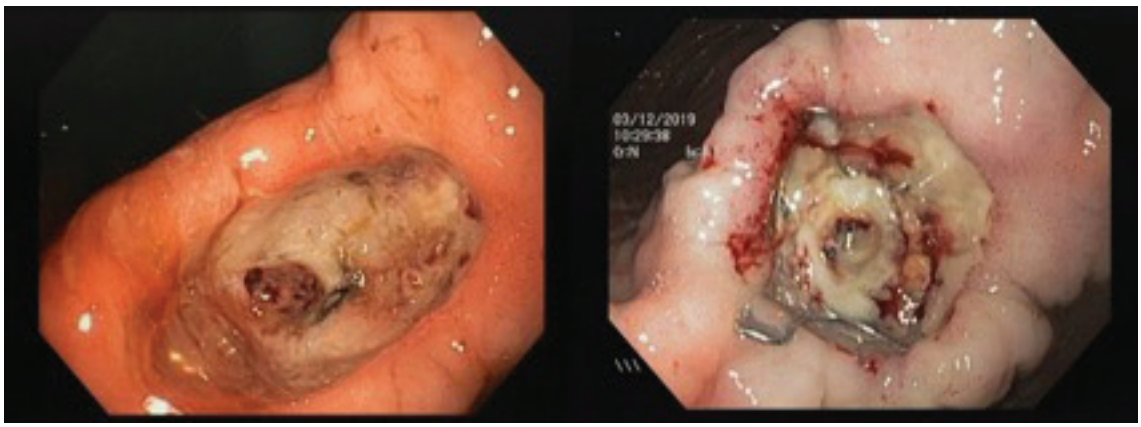


**Figure 14.** Forrest IIa gastric ulcer; Clip over-the-scope (OTSC)

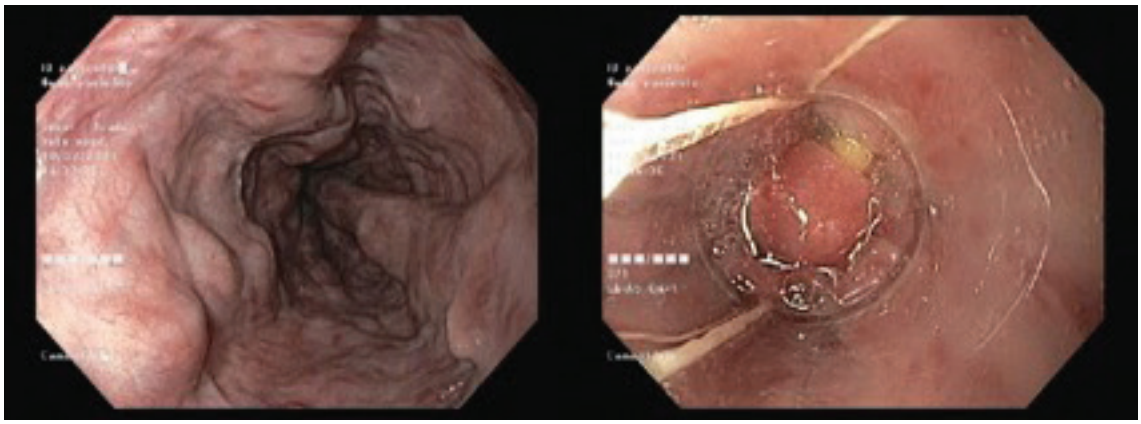


**Figure 15.** Esophageal varices and elastic lacquering

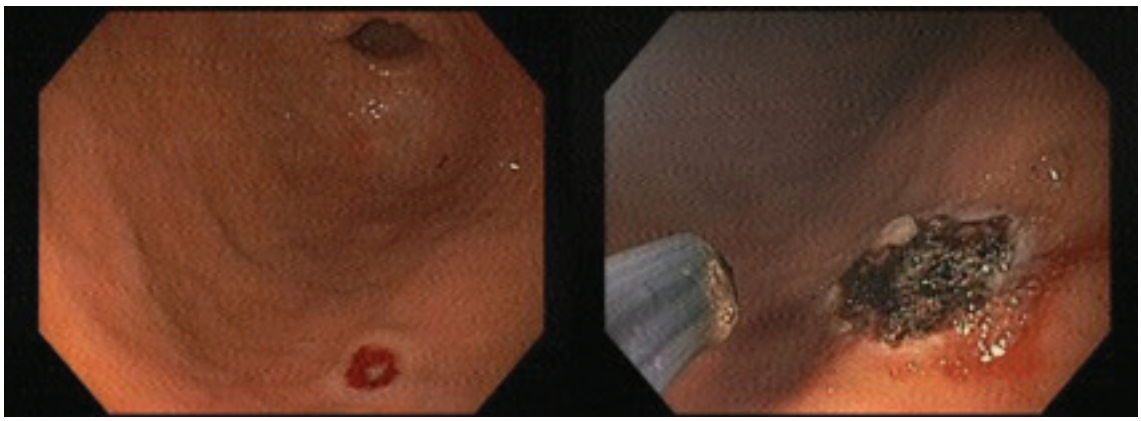
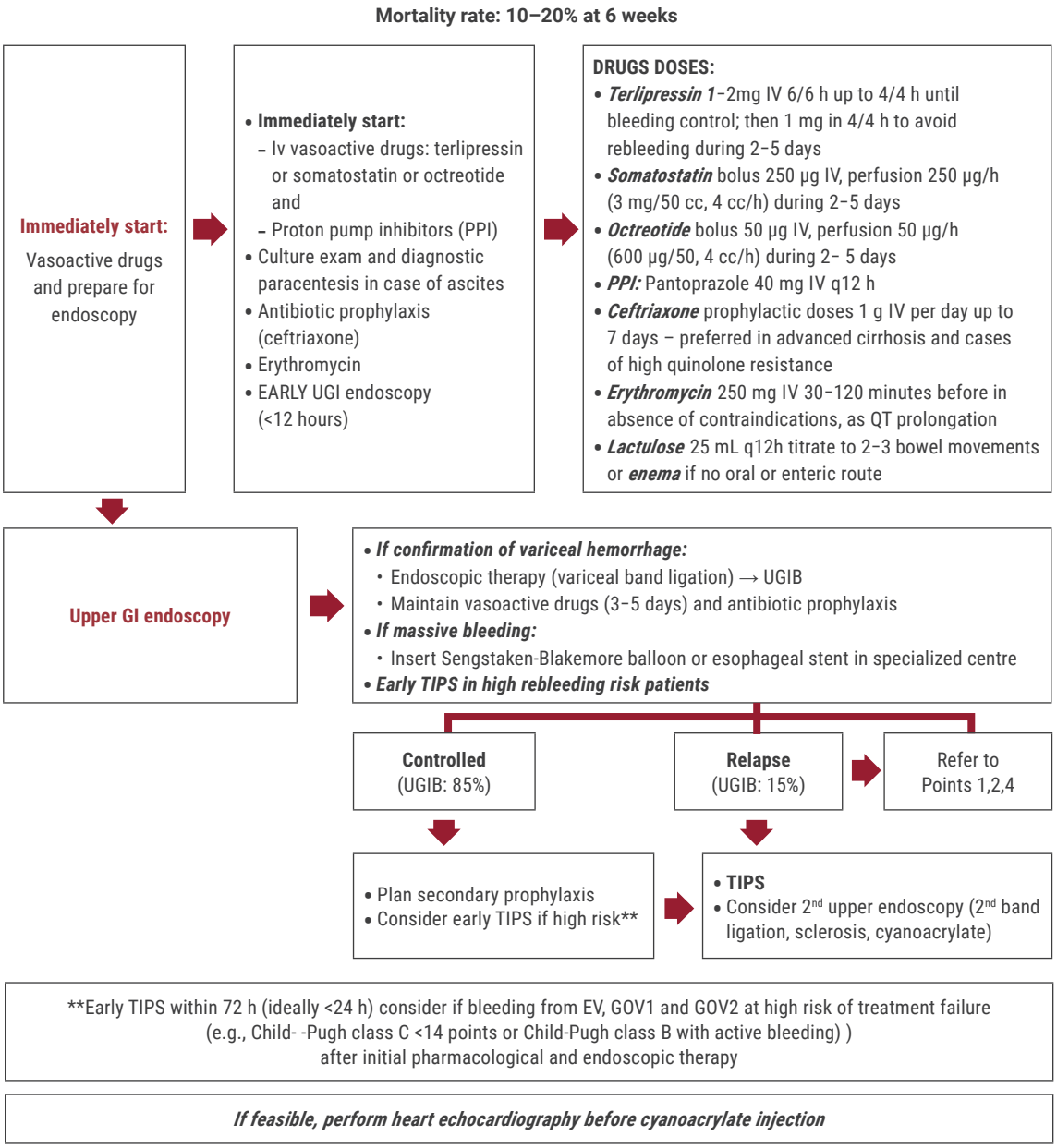


**Figure 16.** Gastric angiodysplasia and argon-plasma therap




EV, esophageal varice; GI, gastrointestinal; GOV1, gastroesophageal varice type 1; GOV2, gastroesophageal varice type 2; h, hour; IV, intravenous; TIPS, transjugular intrahepatic portosystemic shunt; UGI, upper gastrointestinal; UGIB, upper gastrointestinal bleeding.

**Algorithm 3.1.1.** Variceal upper gastrointestinal bleeding[6]

**Prepare for UGI endoscopy and start empiric treatment (PPI)**

**TIMING**
- Ideally within 24 h after hospital admission
- Blatchford score helps to stratify risk
- **Very early (≤12 h) if:**
  - Persistent hemodynamic instability
  - Intrahospital active bleeding signs
  - Contraindication to anticoagulant suspension
- **Early** (up to 24 h) in the remaining conditions

**PREPARATION**
- Nill by mouth
- Erythromycin 250 mg IV and consider gastric lavage
- PPI bolus + perfusion – pantoprazole or esomeprazole 80 mg bolus, then 8 mg/h

**Blatchford Score**

| Points | | | Points |
|---|---|---|---|
| Blood Urea Nitrogen (mg/dL) | | Systolic BP | |
| 18.2–22.3 | 2 | 100–109 | 1 |
| 22.4–27.9 | 3 | 90–99 | 2 |
| | | | |
| | | | |
| 28–69.9 | 4 | <90 | 3 |
| >=70 | 6 | Others | |
| Hb (g/dL) Man/Woman | | Pulse ≥100/min | 1 |
| 12–12.9 / 10–11.9 | 1 | Melena | 1 |
| 10.0–11.9 | 3 | Syncope | 2 |
| <10.0 / <10.0 | 6 | Liver Disease | 2 |
| | | Heart Failure | 2 |

| | |
|---|---|
| **Blatchford Score ≤1** | • No need for urgent endoscopy or inpatient stay<br>• Refer to outpatient clinic and late endoscopy (≥24 hours). If not practical in due time, consider inpatient stay |
| **Blatchford Score >1 (≥7 predicts the need for endoscopic therapy)** | **Prepare UGI endoscopy and start empiric pharmacological management:**<br>• Nill by mouth<br>• Erythromycin 250 mg IV and consider gastric lavage<br>• PPI bolus + perfusion – pantoprazole or esomeprazole 80 mg bolus, then 8 mg/h |

**UGI Endoscopy**

- Type of endoscopic lesion and endoscopic stigma of bleeding
- Rockall score helps to stratify risk
- Endoscopic treatment – hemostasis[#]
- Forrest classification, mortality and rebleeding risk

| Rockall Score | Relapse Risk (%) | Death Risk (%) |
|---|---|---|
| 0 | 4.9 | 0 |
| 1 | 3.4 | 0 |
| 2 | 5.3 | 0.2 |
| 3 | 11.2 | 2.9 |
| 4 | 14.1 | 5.3 |
| 5 | 24.1 | 10.8 |
| 6 | 32.9 | 17.3 |
| 7 | 43.8 | 27 |
| ≥8 | 41.8 | 41.1 |

(cont.)

(cont.)

**TYPE OF ENDOSCOPIC LESION AND ENDOSCOPIC STIGMA OF BLEEDING**

**FORREST CLASSIFICATION:**

- **Acute Hemorrhage**
  - Forrest I a: Spurting hemorrhage
  - Forrest I b: Oozing hemorrhage
- **Signs of Recent Hemorrhage**
  - Forrest II a: Non-bleeding visible vessel
  - Forrest II b: Adherent clot
  - Forrest II c: Flat pigmented hematin coffee ground base, on ulcer base
- **Lesions without active bleeding**
  - Forrest III: Lesions without signs of recent hemorrhage or fibrin-covered clean ulcer base

**IF HIGH-RISK REBLLEEDING LESIONS**

- *Forrest Ia, Ib, IIa* – High-risk stigma → endoscopic hemostasis
- *Forrest IIb* → carefull clot removal and hemostasis versus PPI

- INDICATION FOR ENDOSCOPIC HEMOSTATIC TREATMENT#
- DILUTE ADRENALIN INJECTION, BIPOLAR COAGULATION, TTS CLIPS, ARGON PLASMA COAGULATION

**MORTALITY AND REBLEEDING RISK**

- SEE ROCKALL SCORE

**IF AFTER ENDOSCOPIC TREATMENT FIRST REBLEEDING**

- REFER TO PREVIOUS POINTS
- SECOND ENDOSCOPY AND ENDOSCOPIC TREATMENT

**SECOND REBLEEDING**

- REFER TO PREVIOUS POINTS
- CONSIDER ANGIOGRAPHY, SURGERY OR ENDOSCOPIC RESCUE TREATMENT, AS HEMOSPRAY OR OTSC

| Rockall Score | | | | |
|---|---|---|---|---|
| **Variables** | **0** | **1** | **2** | **3** |
| **AGE** | <60 | 60–79 | >80 | |
| **SHOCK** | Absent | Pulse >100<br>SBP >100 | SBP <100 | |
| **COMORBIDITY** | Absent | | Heart failure; ischemic coronary arterial disease; major obesity | Renal failure; liver failure; metastatic cancer |
| **ENDOSCOPIC DIAGNOSIS** | Mallory Weiss | All others diagnoses | Digestive cancer | |
| **BLEEDING EVIDENCE** | Absent | | Active; adherent clot; visible vessel | |

BP, blood pressure; iv, intravenous; h, hour; Hb, hemoglobin; OTSC, over-the-scope clip; PPI, proton pump inhibitor; SBP, systolic blood pressure; TIPS, transjugular intrahepatic portosystemic shunt; TTS, through-the-scope clip; UGI: upper gastrointestinal

**Algorithm 3.1.2.** Non-variceal upper gastrointestinal bleeding[11]

# Sengstaken-Blakemore tube insertion

## Cilénia Baldaia

## Sengstaken-Blakemore tube insertion - Why perform?

Upper endoscopy and hemostatic techniques have virtually abolished the use of balloon tamponade. Despite the potential for serious complications, its use can still be very helpful, allowing temporary control of bleeding until the patient is transferred to a facility with endoscopic capabilities, or lifesaving, when all hemostatic measures are unsuccessful. Therefore, the authors decided to describe this rare procedure.

Balloon tamponade is generally a temporizing measure and should not be used for more than 24 hours.

Minnesota tube, or modified Sengstaken-Blakemore (SB) tube, is a four-lumen tube with an additional lumen to aspirate esophageal lumen to prevent aspiration.

ELLA stent is an alternative method for esophageal varices tamponade, but does not control fundic varices, a potential source of life-threatening bleeding.

## Sengstaken-Blakemore tube insertion – How to perform?

### Materials:

- SB tube is normally kept in the freezer, as it becomes stiffer and helps insertion.
- Three syringes are used: two for suctioning the esophageal and gastric lumen, and one for inflating the gastric balloon.
- Metal artery forceps are used for clamping the balloon ports.

- To inflate the esophageal balloon, the following materials should be prepared to evaluate pressure:
  - a 50cc Luer Lock syringe;
  - an adaptor with a conical end that will fit into the esophageal port; the Luer Lock end will fit into the sphygmomanometer;
  - a three-way valve;
  - a sphygmomanometer with detachable arm cuff to remove it and fit the Luer Lock end of the adaptor.

## Technique:

- First and foremost: Do not forget airway protection - patients requiring balloon tamponade should also usually be intubated. It is particularly important in cases of encephalopathy, $Sat0_2$ <90%, and aspiration pneumonia.
- If possible, aspirate the stomach or use prokinetics.
- Position the patient as for a normal endoscopy.
- Before insertion, check the balloons by inflating air and checking for any leak. Contrast mixed water is an alternative for some. If the patient will be air transported, the balloons should be filled with water.
- Coat the balloons on the tube with water-soluble lubricating jelly. Pass the tube at least to the 50-cm mark. The tube can be passed through the nostrils or preferably through the mouth. Oral route is the preferred in intubated patients.

Sometimes the tube is very difficult to insert, and a laryngoscope and Magill's forceps may be required to guide it past the cricopharyngeal muscle.

- Once it has gone up to the 50-cm mark, confirm that the tip is in the gastric lumen by aspirating the stomach content and auscultating over the stomach. In cases of uncertainty, obtain a portable chest x-ray.
- Once sure that the tip is in the stomach, inflate the gastric balloon with 200 mL of air (putting two artery forceps as clamp and inserting the pegs supplied with the tube) and gently tug it;
- *Attention: Clamp the tube(s) in between air filling(s).*
- *Attention: Never inflate the esophageal balloon before the gastric balloon.*
- Pull the tube with the inflated gastric balloon back gently until resistance is felt against the diaphragm.

- For most patients, gastric balloon inflation and traction is enough to stop the variceal hemorrhage. If bleeding persists, the esophageal balloon will be inflated. For some patients, gastric and esophageal balloons will both remain inflated.
- Attention: inflate the esophageal balloon to the lowest pressure required to stop bleeding (usually 30-45 mmHg), then clamp the port for the esophageal balloon. Check the balloon pressure periodically.
- Secure the proximal end of the tube using a traction device. A pulley device can be used to maintain the desired 0.45-0.9 Kg of traction. A 500-mL bag of intravenous fluid can serve as initial weight. If the tube has been inserted through the nostrils, a foam rubber cuff, which is generally included in the tube package, can be used to maintain traction against the nose.
- Finally, fix the tube and keep record of the distance between the tip and the incisor teeth (usually around the 30-35-cm mark).

### Aftercare and removal:

- Migration of the gastric balloon into the esophagus can cause compression of the trachea and respiratory distress. In case of emergency, cut the gastric balloon port to let the air escape.
- Suction both esophageal and gastric lumen at intervals of 10 minutes, increasing to 30 minutes and then to one hour after stabilization.
- Frequent oropharyngeal suction is very important.
- Do not forget antibiotic prophylaxis and continued vasoactive drugs.
- In absence of bleeding, relieve pressure in the esophageal balloon (for example, for 10 minutes every 2 hours) to prevent pressure necrosis.
- Repeat endoscopy as soon as possible, up to 24 hours. Consider alternative methods to control portal hypertension, as transjugular intrahepatic portosystemic shunt (TIPS).
- The Sengstaken tube should be removed in the endoscopy room. Remember that the chance of rebleeding when balloon is deflated is high. Be prepared to treat!
- First deflate the esophageal balloon, then take off the traction, and finally remove the tube

## Troubleshooting and complications

To control bleeding, the gastric balloon must be positioned close to the gastroesophageal junction and adequately inflated, fixed, and with sustained traction.

Factors related with increased risk of complications include (i) inflating the gastric balloon within the esophagus (risk of esophageal rupture); (ii) inadequately filling the gastric balloon (<100 mL allows the tube to move upwards into the esophagus, increasing the risk of larynx occlusion and pulmonary aspiration); (iii) inflating the esophageal balloon at the larynx level; and (iv) using excessive mechanical traction (>1 Kg) or applying inflation for prolonged periods (>36 hours).

## Complications

- Aspiration is probably the most frequent major complication of SB tube insertion, with the greatest risk occurring during insertion. To prevent it, aspirate the stomach and use prokinetics prior to SB placement. Most importantly, use a low threshold for .
- Asphyxiation by proximal tube migration can be prevented with endotracheal intubation. If it occurs, emergency cutting across all tube lumens distal to bifurcation points allows immediate extraction of the entire tube.
- Esophageal perforation or rupture can occur in cases of gastric balloon inflation in the esophagus or be secondary to esophageal mucosal necrosis resulting from excessive or prolonged esophageal balloon inflation.
- Tracheal rupture.
- Minor complications include pain, pharyngeal and gastroesophageal erosions and ulcers, pressure necrosis of the nose, lips, and tongue, facial skin pressure ulcers, and hiccups.

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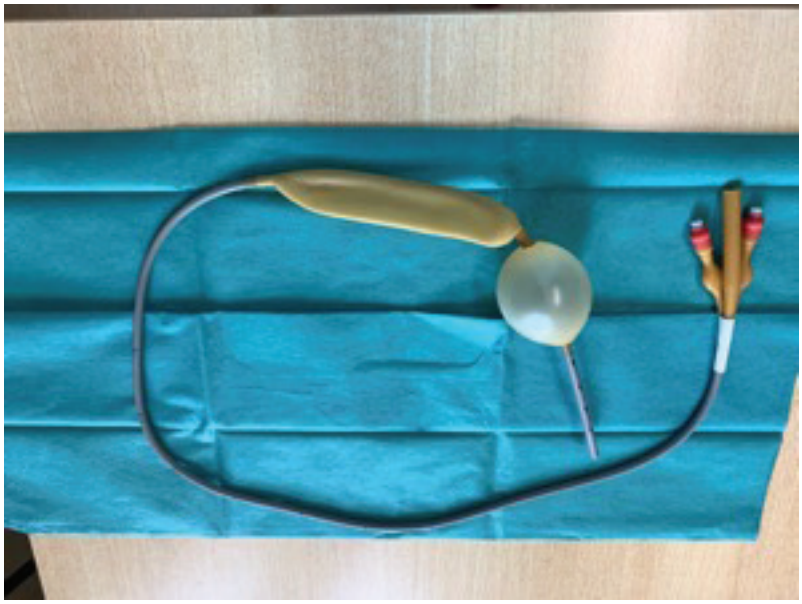

**Figure 1.** Sengstaken-Blakemore tube

# Lower gastrointestinal bleeding

## Nuno Almeida, Catarina Correia

Acute lower gastrointestinal bleeding (LGIB) refers to blood loss of recent onset originating from the colon and/or rectum. It presents as hematochezia in most cases, but bleeding from the right colon can also present as melena. Its annual incidence is 33–87 cases/100,000 individuals, and most patients are older than 70 years.[1–3] Bleeding stops spontaneously in 80–85% of cases and mortality rate is 2–4% (although higher in older patients and in those with comorbidities).[4–6] Death due to severe bleeding occurs in less than 1% of cases.[3,7]

Upper gastrointestinal bleeding (UGIB) should be considered in patients presenting with hematochezia and orthostasis (a potential severe bleeding), since 15% of these patients have bleeding from a foregut source.[8,9] Such patients should be managed according to the UGIB algorithm, and upper endoscopy is the main diagnostic and therapeutic strategy. It should be remembered that individuals with a history of peptic ulcer disease or liver disturbance/portal hypertension and those using antiplatelet or anticoagulants are at higher risk of UGIB.[8,10,11]

Considering etiology, diverticulosis is the most common cause of acute LGIB (Figure 1).[12] Other potential causes include colonic polyps and cancer, colitis (ischemic [Figure 4], infectious, noninfectious – as radiation [Figures 2 and 3] –, inflammatory bowel diseases), angiectasia, postpolypectomy (Figure 5), rectal ulcer, hemorrhoids, anal fissure, or others, including Dieulafoy lesion and colonic or rectal varices.[13] Determining the bleeding source is challenging, and 23-50% of patients are discharged without a definitive diagnosis.[7,14] This number decreases to 9% in patients submitted to colonoscopy.[3]

According to the American College of Gastroenterology guidelines, initial patient assessment and hemodynamic resuscitation should be simultaneously performed.[4] A focused history, physical examination, and laboratory evaluation should be obtained at the time of patient presentation, and the severity, possible location, and etiology of bleeding determined.[4] During this evaluation, it is of paramount importance to determine heart rate and blood pressure, to obtain hemoglobin level, prothrombin time, blood urea nitrogen (BUN), and creatinine. Rectal digital examination is mandatory, since it can detect potential anorectal hemorrhage sources and allows a better assessment of stool characteristics.[4]

If BUN/creatinine ratio is higher than 30, UGIB should be considered, and proceedings performed as previously described in this book.[15] Previous studies suggested that nasogastric lavage/aspirate could be useful in such cases to determine the bleeding location, but it should be noted that a negative aspirate does not completely exclude UGIB, and in most cases an upper endoscopy should be performed.[10,16,17] Recent evidence suggests that nasogastric tube placement in suspected UGIB should not be routinely recommended.[18,19]

The Oakland score should also be estimated and the presence of risk factors for poor outcomes should be considered. Regarding the latter, different studies have identified multiple risk factors, including:[4,20–24]

- Hemodynamic instability on admission:
    - Heart rate >100 bpm.
    - Systolic blood pressure <100 mm/Hg.
    - Syncope.
- Persistent bleeding.
- Rebleeding.
- Nontender abdomen.
- History of diverticulosis or angiectasia.
- High Charlson comorbidity index.
- Age >60 years.
- Laboratory alterations:
    - Creatinine >1.7 mg/dL.
    - Hematocrit <35%.
    - Prothrombin time >1.2 control.
    - Hypoalbuminemia.
- Current aspirin use.

A simple score, such as the BLEED score, can be used in the clinical practice. It comprises five variables: ongoing fresh bleeding, low systolic blood pressure (<100 mmHg), elevated prothrombin time (>1.2x the control), erratic/altered mental status, and unstable comorbid illness (any organ system abnormality that would ordinarily require Intensive Care Unit [ICU] admission).[21] Patients with any of these criteria are classified as high-risk and should be preferentially managed in Intensive Care Unit (ICU).

Other scores are in place, including the NOBLADS, Strate, Sengupta, ABC, Birmingham, Severe Acute LGIB, and HAKA scores.[22,25–31] Scores for UGIB can also be used in LGIB.[25] A study comparing these scores determined that AIMS-65 and Rockall scores were the strongest predictors of death, and the Glasgow-Blatchford and Oakland scores were appropriate to determine the rebleeding risk.[32] However, no score reliably predicted the need of intervention to resolve bleeding.[32]

Severe lower GIB is defined as continued bleeding within the first 24 hours of hospitalization (transfusion of 2 or more units of packed red blood cells and/or an hematocrit value drop of 20% or more) and/or recurrent bleeding after 24 hours of stability (need for additional

transfusions, further hematocrit value drop of 20% or more, or hospital readmission for lower GIB within 1 week of discharge).[13]

The prognostic score proposed by Strate L et al. applies one point to each risk factor: aspirin use, more than two comorbid illnesses, heart rate ≥100 bpm, nontender abdominal examination, rectal bleeding within the first four hours of evaluation, syncope, and systolic blood pressure ≤ 115 mmHg.[20] Patients with 1–3 points or ≥4 points have a 43% and 79% risk of presenting with severe bleeding, respectively.[20] These patients must be admitted to ICU and managed accordingly.[4]

Considering resuscitation and management of coagulation defects, general rules for all GI hemorrhages should be followed (previously described in this book). Identifying the source of bleeding is a clinical priority after successful hemodynamic resuscitation, and not as straightforward as in UGIB.[33] Colonoscopy should be the procedure of choice for almost all patients, since it allows diagnosis, tissue sampling, and specific treatment.[4] It should be performed after adequate colon cleansing with 4–6 liters of polyethylene glycol-based solution or the equivalent.[11,34,35] Colonoscopy has diagnostic and therapeutic purposes, and a diagnostic yield in this specific setting of 45–100%.[11,34,36,37] Unprepped sigmoidoscopy or colonoscopy is not recommended in acute LGIB setting.[4,38] In high-risk patients with ongoing bleeding who are intolerant to oral intake and at low risk of aspiration, administration of bowel preparation through a nasogastric tube can be considered.[4]

The timing of colonoscopy depends on the patient's hemodynamic status. The first approach is to calculate the shock index (SI), corresponding to the ratio between heart rate and systolic blood pressure.[33] Importantly, it should be remembered that SI is affected by ß-blockers.

A positive SI (≥1) is a marker of active bleeding, and the patient is classified as unstable.[33,39] In cases of strong suspicion of UGIB, an upper GI endoscopy should be performed, if feasible. When upper GI endoscopy is not feasible or deemed unnecessary, the indication is for CT angiography (CTA), since it has a sensitivity of 79-95% and specificity of 95-100%.[33,40,41] After positive CTA, specific treatment should be implemented as soon as possible, either by intervention radiology (angiography with embolization) or an endoscopic method (upper or lower GIB).[33] If the initial treatment method fails, a second option can be considered (intervention radiology and/or endoscopic attempt) before referral to surgery. If CTA does not reveal the source of bleeding, the patient must be admitted for LGI endoscopy.

Patients with negative SI (<1) are classified as stable, and in these cases, risk is assessed by the Oakland score (Table 1).[7,32] This score includes seven variables that should be measured during initial clinical assessment: age, gender, previous hospital admission for LGIB, digital rectal examination findings, heart rate, systolic blood pressure, and hemoglobin. It should be noted that the Oakland score is validated for use in the United Kingdom only.[7] The Glasgow-Blatchford score, usually used for UGIB, can also identify patients with LGIB at risk of adverse outcomes.[32,33]

A score ≤8 indicates minor bleeding, and the patient can be discharged for outpatient management with a 95% degree of confidence.[33] However, these patients must be submitted to elective colonoscopy, ideally in the first two weeks after discharge.[33]

If the Oakland score is >8, the patient should be admitted for observation and further study.[33] Again, upper GI endoscopy should be considered in cases of clinical suspicion of UGIB and/or BUN/creatinine >30. If the patient has bright rectal bleeding, anorectal inspection by proctoscopy or flexible sigmoidoscopy should be considered, since benign anorectal conditions account for more than 15% of cases.[7] In all other cases, colonoscopy is mandatory after adequate bowel cleansing, and the endoscopist should try to intubate the terminal ileum. Administration of a prokinetic/antiemetic agents immediately before initiating colon preparation should also be considered.[4] In patients with high-risk clinical features and/or signs or symptoms of ongoing bleeding, colonoscopy should be performed within the first 24 hours.[4,35] In patients without high-risk clinical features or serious comorbid diseases, and in those with high-risk clinical features without signs or symptoms of ongoing bleeding, colonoscopy should be performed on the next available list.[4] In fact, few studies have addressed the time interval for colonoscopy, and those comparing urgent (<24 hours) with elective colonoscopy have often been contradictory, namely regarding clinical outcomes, as rebleeding or need for surgery.[8,42–46]

Colonoscopy complications in LGIB range from 0.3% to 1.3%.[47] Bowel perforation, aspiration pneumonia, and volume overload due to bowel preparation are specific risks in this setting.[38]

If no diagnosis is established after the above-mentioned endoscopic and radiological investigations and further bleeding episodes occur, red cell scintigraphy and/or capsule endoscopy should be considered.[33]

Although most LGIB cases spontaneously resolve, three main therapeutic options are in place: endoscopy, transcatheter mesenteric embolization, and surgery.[33]

Endoscopic therapy is indicated in patients with high-risk endoscopic stigmata of bleeding: active bleeding (spurting and oozing), non-bleeding visible vessel (Figure 6), or adherent clot.[4] Diverticulosis, angiectasia, and post-polypectomy bleeding are the conditions most likely to benefit from endoscopic treatment.

There are three main types of endoscopic therapy:

- Pharmacological – dilute adrenalin injection (1/10,000 to 1/20,000 dilution); hemostatic topical spray/powder; sclerosing agents (conditional use).
- Thermal – bipolar coagulation; argon plasma coagulation.
- Mechanical – endoscopic through-the-scope hemoclips; over-the-scope clips; band ligation.

Since the colon wall is thin, special care must be taken during such therapies to avoid perforation. Due to the unpredictable depth of tissue injury they may cause, sclerosing agents are generally avoided for non-variceal lesions. Thermal methods have also an increased risk of perforation.

If no bowel purge has been performed and thermal therapy or diathermy is considered, the risk of colonic explosion should be taken into account. In such circumstances, these therapies should only be used if considered essential, and $CO_2$ with gas exchange should be available to reduce the risk of this serious complication.[33]

Epinephrine injection should always be used with a second hemostasis modality, since its effect is short-living.[4,33]

After endoscopic treatment of some lesions, mainly diverticulum or Dieulafoy lesions, an India ink tattoo or clip should be placed to assist in re-localization if rebleeding occurs.[35] Early rebleeding after urgent colonoscopy occurs in 22% of cases, and late rebleeding in 16%.[8,11] A second endoscopic examination with hemostasis should be considered in those circumstances.[4]

Angiographic embolization is a valid first or second option, especially if CTA reveals extravasation.[4,33,35] It has a technical success rate of 93–100%, but 7–24% of patients develop complications, with bowel ischemia being the most feared.[48–56] The risk of rebleeding is also relevant, being of 10–50% in the short term and 25% at 2 years.[57] The risk of contrast-induced nephropathy (by CTA and/or angiography) also exists, and standard precautions should be taken to avoid it.[4] The typical patient candidate for endovascular therapy presents with massive bleeding, failure to respond to conservative medical therapy, and hemorrhage that does not respond or recurs after one or two attempts of endoscopic control.[58]

Surgery for LGIB is rarely required, and should be reserved for the minority of patients with persistent or refractory bleeding despite endoscopic and radiologic interventions.[4,33,35] No patient should proceed to emergency laparotomy unless every effort has been made to localize the bleeding by the above-mentioned techniques.[33]

Cirrhotic patients represent a specific subgroup. Data on LGIB in this patient population is very limited, but this form of GI hemorrhage may be associated with life-threatening complications similar to those observed in UGIB.[59] Morbidity and mortality factors in cirrhotic patients with LGIB include advanced Child-Pugh and portal hypertension, coagulopathy, comorbid diseases, and polypharmacy.[59]

The most common causes of LGIB in these patients are portal hypertensive colopathy, colorectal varices, and hemorrhoids,[59] but all other causes of LGIB are also possible.

The prevalence of rectal varices in cirrhotic patients is 38–56%, while clinically significant bleeding is rare and occurs in 0.5–5% of cases.[60–62]

Initial management follows the same rules previously described for variceal UGIB.[59,63] Three treatment options are available: endoscopic, radiologic, and surgical approach.

The endoscopic treatment of colonic or rectal varices can involve direct sclerosis, band ligation, or cyanoacrylate injection.[63] The most serious adverse events of glue injection are systemic embolization and sepsis. The former complication is more likely in cases with patent foramen ovale or arteriovenous pulmonary shunt.[64] Heart echocardiography, if feasible, can be useful in diminishing such risks.

Transjugular intrahepatic portosystemic shunt, with or without embolization, can be considered in patients with endoscopic failure or at high risk of rebleeding.[63] Surgical treatment is currently very rare in the clinical practice, as these patients are not good surgical candidates.

| **Table 1. Oakland score** | |
|---|---|
| Predictor | Score component value |
| Age (years) | |
| <40 | 0 |
| 40–69 | 1 |
| ≥70 | 2 |
| Gender | |
| Female | 0 |
| Male | 1 |
| Previous LGIB admission | |
| No 0 | 0 |
| Yes 1 | 1 |
| Digital rectal examination findings | |
| No blood | 0 |
| Blood | 1 |
| Heart rate (bpm) | |
| <70 | 0 |
| 70–89 | 1 |
| 90–109 | 2 |
| ≥110 | 3 |
| Systolic blood pressure (mm Hg) | |
| <90 | 5 |
| 90–119 | 4 |
| 120–129 | 3 |
| 130–159 | 2 |
| ≥160 | 0 |
| Hemoglobin (g/L) | |
| <70 | 22 |
| 70–89 | 17 |
| 90–109 | 13 |
| 110–129 | 8 |
| 130–159 | 4 |
| ≥160 | 0 |

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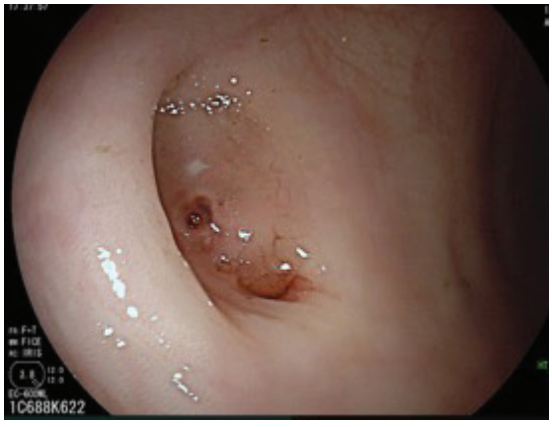



**Figure 1.** Diverticulum with a visible vessel

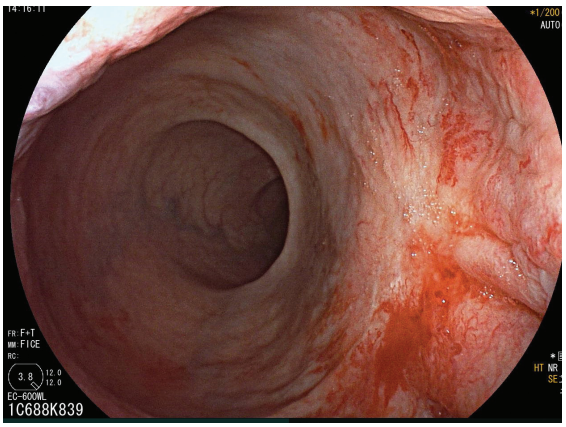



**Figure 2.** Radiation proctitis in a patient with prostate carcinoma

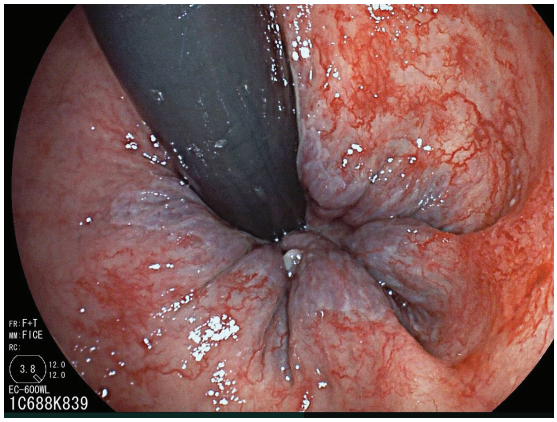



**Figure 3.** Radiation proctitis in a patient with prostate carcinoma (with the colonoscope inverted in the rectum)

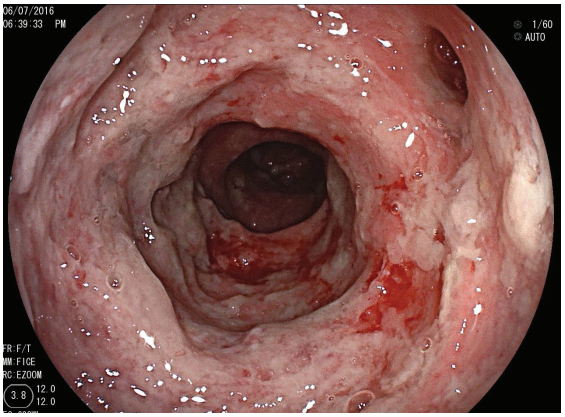



**Figure 4.** Severe ischemic colitis

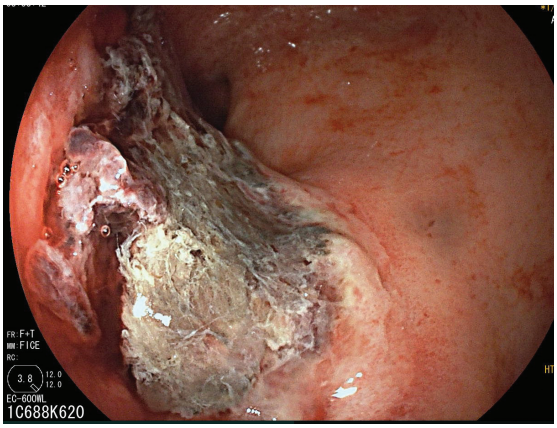



**Figure 5.** Bleeding after submucosal dissection of a rectal lesion

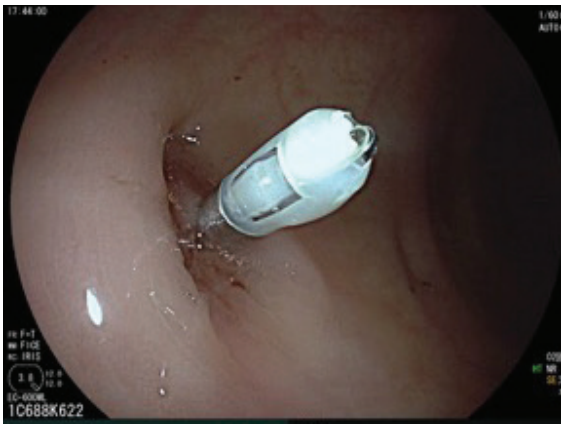



**Figure 6.** Endoscopic hemostasis with clip in a non-bleeding vessel in a diverticulum (see Figure 1)

**Resuscitation and Risk Assessment**

**CLINICAL HISTORY AND PHYSICAL EXAMINATION**
- Rectal digital examination is mandatory
- **Assess severity:**
  - Heart rate
  - Blood pressure (BP)
  - Blood tests
    - *Hemoglobin*
    - *Prothrombin time*
    - *BUN and creatinine:*
    - BUN/Creatinine >30
      - consider UGIB
- Calculate Oakland scorel
- Risk factor for poor outcome

**Risk factors for poor outcome – consider ICU admission**
- Hemodynamic instability at admission
  - *Heart rate >100*
  - *Systolic BP <100 mm/Hg*
  - *Syncope*
- Persistent bleeding
- Rebleeding
- Non-tender abdomen
- History of diverticulosis or angiectasia
- High Charlson comorbidity index
- Age >60 years
- Laboratory alterations
  - *Creatinine >1.7 mg/dL*
  - *Hematocrit <35%*
  - *PT >1.2 control*
  - *Hypoalbuminemia*
- Current aspirin use

**Oakland Score**

| | Points | | Points |
|---|---|---|---|
| Age (years) | | Systolic BP (mmHg) | |
| <40 | 0 | <90 | 5 |
| 40–69 | 1 | 90–119 | 4 |
| ≥70 | 2 | 120–129 | 3 |
| Gender | | 130–159 | 2 |
| Female | 0 | ≥160 | 0 |
| Male | 1 | Hemoglobin (g/dL) | |
| Previous LGIB admission | | <7 | 22 |
| No | 0 | 7–8.9 | 17 |
| Yes | 1 | 9–10.9 | 13 |
| DRE Findings | | 11–12.9 | 8 |
| No blood | 0 | 13–15.9 | 4 |
| Blood | 1 | ≥16 | 0 |
| | | Heart Rate (bpm) | |
| | | <70 | 0 |
| | | 70–89 | 1 |
| | | 90–109 | 2 |
| | | ≥110 | 3 |

**Oakland Score ≤ 8**
- With no other indications for hospital admission
- Suitable for immediate discharge and outpatient investigation

**Oakland Score > 8**
- Prepare lower endoscopy

**Calculate shock index (Heart rate/ systolic blood pressure)**

**>1 – Unstable GI bleeding or suspected active bleeding**
- ***Consider UGIB*** – UGI endoscopy, if feasible (if patient is stable after initial resuscitation)
  - **If positive** – manage as appropriate (4)
- *Perform CT angiogram* (CTA) (if UGI endoscopy not feasible or deemed unnecessary)
  - **If positive** - Treatment with intervention radiology or endoscopic method
    - Success – consider elective upper or lower GI (LGI) endoscopy
    - Failure – consider intervention radiology (after endoscopic attempt) or surgery
  - **If negative:** Admit for LGI endoscopy

**<1 – Stable GI bleeding**

***Calculate Oakland risk score***
- **Minor bleeding (Oakland ≤8):** Discharge – investigation in outpatient setting
- **Major bleeding (Oakland >8)**
  - Consider UGI endoscopy (15% of suspected LGIB cases correspond to UGIB)
  - If bright rectal bleeding, consider anorectal inspection
  - Admit for colonoscopy after antegrade preparation
    - Ongoing bleeding and/or risk factors - <24 hours
    - Not ongoing bleeding and/or no risk factors – next available list
      - If a lesion is found – treat endoscopically
      - If no lesion is found:
        - Further bleeding: CTA, capsule endoscopy RBC scintigraphy
        - No further bleeding – discharge and follow-up

**BLEED (variables)**

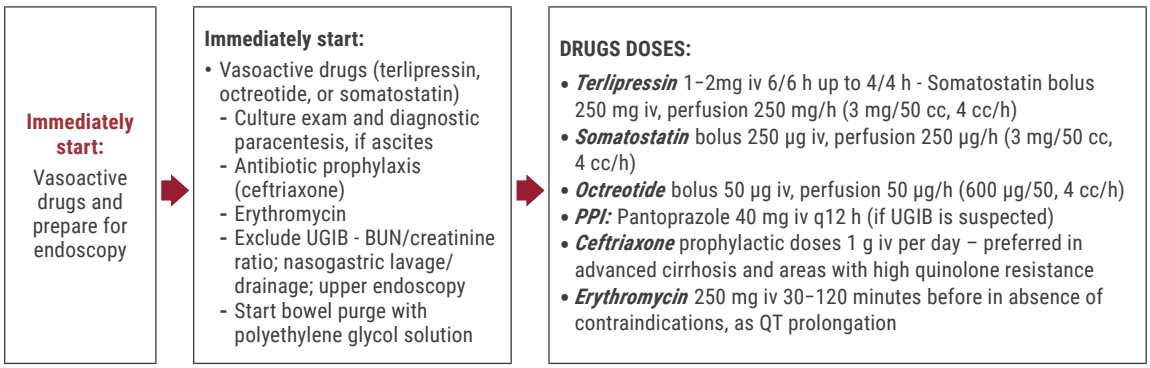
| |
|---|
| Ongoing bleeding |
| SBP <100 mmHg |
| Prothrombin time >1.2 control |
| Altered mental status |
| Unstable comorbid illness (any organ system abnormality that ordinarily would require ICU admission) |

**LGI endoscopy**
- Type of endoscopic lesion and endoscopic stigmata of bleeding
- Endoscopic treatment – hemostasis**
- BLEED – rebleeding and mortality risk

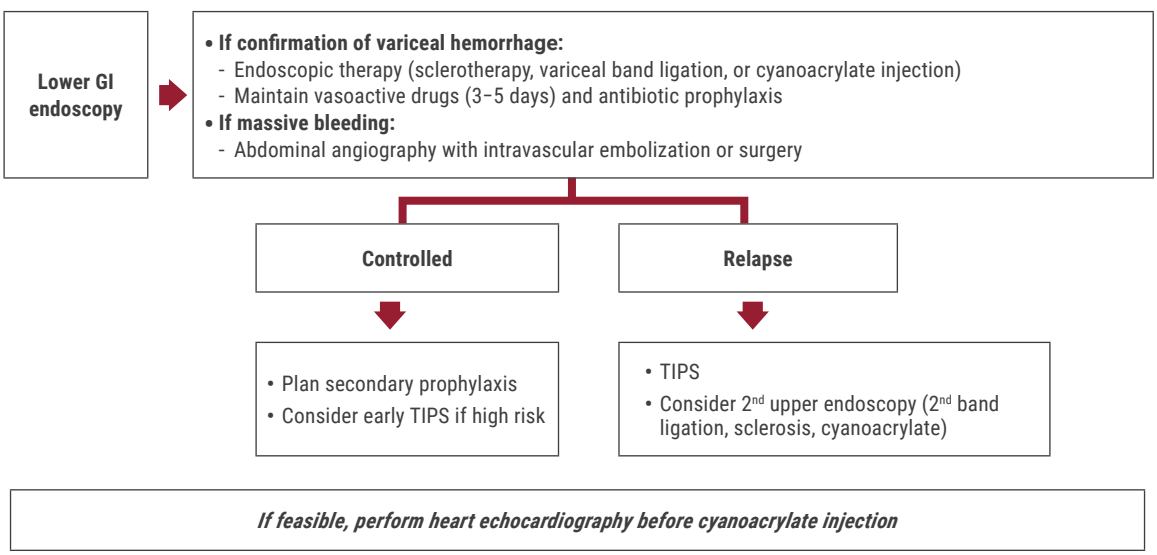
| | |
|---|---|
| **TYPE OF ENDOSCOPIC LESION AND ENDOSCOPIC STIGMA OF BLEEDING** | • Diverticula with active bleeding<br>• Bleeding hemorrhoids<br>• Anal fissure<br>• Polyps/Post-polypectomy<br>• Carcinoma<br>• Angiodysplasia<br>• Dieulafoy lesion<br>• Rectal or colonic ulcers<br>• Active colitis (ischemic, infectious, inflammatory, radiation-induced) |
| **IF HIGH-RISK REBLEEDING LESIONS** | • Indication for endoscopic hemostatic treatment: **<br>• Pharmacological – Dilute adrenalin injection; sclerosing agents (conditional use)<br>• Thermal – bipolar coagulation, argon plasma coagulation<br>• Mechanical – endoscopic hemoclips; ligation |
| **MORTALITY AND REBLEEDING RISK** | • See BLEED |
| **FIRST REBLEEDING AFTER SUCCESSFUL ENDOSCOPIC TREATMENT** | • Refer to previous points<br>• Second endoscop and endoscopic treatment<br>• Consider angiography or surgery if endoscopic failure |
| **SECOND REBLEEDING** | • Refer to previous points<br>• Consider angiography, surgery or endoscopic rescue treatment as hemospray or OTSC |
| **"RED FLAGS"** | • For endoscopic treatment, mechanical methods are preferable (higher risk of perforaon with thermal methods)<br>• Surgery without previous idenficaon of the bleeding source or, at least, of the exact locaon of bleeding must be the last resource – high mortality risk |

BP, blood pressure; BUN, blood urea nitrogen; CT, computerized tomography; CTA, CT angiography; DRE, digital rectal exam; GI, gastrointestinal; ICU, Intensive Care Unit; LGI, lower GI; OTSC, over-the-scope clip; PT, prothrombin time; RBC, red blood cell; SBP, systolic blood pressure; UGI, upper GI; UGIB, upper gastrointestinal bleeding.

**Algorithm 3.2.** Lower gastrointestinal bleeding[33]




**Algorithm 3.2.1.** Suspected variceal lower gastrointestinal bleeding[33,65]




BUN, blood urea nitrogen; GI, gastrointestinal; h, hour; iv, intravenous; TIPS, transjugular intrahepatic portosystemic shunt; UGIB, upper gastrointestinal bleeding

**Algorithm 3.2.2.** Variceal lower gastrointestinal bleeding[33,65]

# Mid gastrointestinal bleeding

## Nuno Almeida, Catarina Correia

Historically, GI bleeding was classified as upper and lower if the bleeding source was located above or beyond the ligament of Treitz, respectively.[1] Nowadays, GI bleeding is now classified in three different types: upper (UGIB), middle (MGIB) and lower (LGIB).[2] MGIB refers to hemorrhage from the papilla of Vater through ileocecal valve (small bowel bleeding) and represents 5 to 10% of all GI bleeding.[3,4] It replaced the older term obscure GI bleeding that is now reserved for patients in whom a source of bleeding cannot be identified anywhere in the GI tract after standard upper and lower endoscopy, capsule endoscopy (CE) and/or enteroscopy and radiographic testing.[5]

In a patient with overt GI bleeding with no hemorrhagic lesion identified after upper endoscopy and colonoscopy a small bowel bleeding must be taken into account. This type of hemorrhage represents 5 to 10% of all GI bleedings.[5,6] It was previously designed as "obscure", but this term is now reserved for cases in which a source of hemorrhage has not been identified after a thorough examination of the entire gastrointestinal tract, including the small bowel.[5]

Concerning small bowel bleeding we must consider multiple etiologies: vascular lesions (angiodysplasia – Figure 1; Dieulafoy's lesion); inflammatory bowel disease – Figure 2, Meckel's diverticulum; small bowel neoplasms – Figure 3; erosions or ulcers related to nonsteroidal anti-inflammatory drugs; aortoenteric fistula; radiation enteropathy; small bowel varices.[5] A careful clinical history can suggest etiology: aortic stenosis – Heyde syndrome; family history of cancer at an early age – Lynch syndrome; telangiectasias of lips and/or oropharynx – Rendu-Osler-Weber syndrome; dermatitis herpetiformis – Celiac disease; history of abdominal aortic aneurisma repair – aortoenteric fistula.[5,7] Age and ethnic background are major determinants in etiology.[5] It is important to highlight that angiodysplasias are the commonest causes of MGIB in Western countries.[8-10]

Fortunately, most patients with suspected MGIB are hemodynamically stable since bleeding from the small bowel is rarely arterial.[1,5] However, there are some rare exceptions, such as aortoenteric fistula, Dieulafoy's lesion and small bowel diverticular bleeding.[1] Ectopic small bowel varices can also be a source of massive bleeding, but such pathology is, fortunately, rare.[1] This influences our approach to such patients, allowing time to perform a thorough clinical history. Besides that, multiple diagnostic investigations are now available.

In patients with suspected mid-GI bleeding a second-look upper endoscopy and/or colonoscopy should be considered, even if the scientific evidence supporting such recommendation is of low or very low level.[5,11] Second-look examinations have been associated with diagnostic

yields of 3% to 60%, particularly concerning upper endoscopy.[12] In fact, in 75% of cases the source is in the small bowel, but the remainder are due to missed lesions in either the upper or lower endoscopic examination.[13-15] If second-look upper endoscopy is deemed necessary, a push enteroscopy is a valuable alternative.[16] The diagnostic yield of such technique range from 3 to 70%.[5,17–19] It is important to notice that push enteroscopy has a lower diagnostic yield compared to capsule endoscopy (CE) and is not recommended as a first-line investigation in patients with suspected small bowel hemorrhage.[11] It can only be undertaken as an alternative to a second-look upper endoscopy.

After negative upper and lower endoscopy, a small bowel study must be implemented. Once more, hemodynamic status determines the technique of choice (16). If the patient is unstable some authors traditionally recommended abdominal angiography with embolization, if feasible.[12] However, more recent evidence suggests that such intervention should be preceded by multiphasic CT (CT angiography - CTA) that is a potential first-line tool for evaluation of all acute GI bleeding episodes (5,16,20). In a meta-analysis it had a pooled sensitivity of 89% and a specificity of 85%.[21] CTA is able to depict bleeding at a rate of 0.3-0.5 mL/min and should be performed as soon as possible, since a lengthening time between the start of hemorrhage and the radiological examination decreases its' sensitivity.[20] The main candidates for CTA are unstable patients who respond to resuscitation and stable patients who have risk factors for being actively bleeding.[20]

However, if the patient has a rapid active hemorrhage and do not respond appropriately to resuscitation the best method is direct fluoroscopic angiography, since it has the capability of immediate diagnosis and treatment. Angiography has a mean diagnostic yield of 50%, considering all GI tract.[5] Embolization of vascular supply can be made with coils, polyvinyl alcohol beads, glue and/or gelatin sponges. Its' main complication is bowel ischemia, that can occur in up to 3 to 20% of patients.[20,22] Other complications beyond thromboembolic events include renal failure and infection or bleeding at the catheter site.[5] Optimally, patients proposed for angiography should had a serum creatinine less than 1.5 mg/dL, an estimated glomerular filtration rate higher than 60 mL/min/1.73 $m^2$, an international normalized ratio lower than 1.5 and a platelet count greater that 50,000/$mm^3$.[23]

In stable patients CE is the best tool to examine the small bowel and it should be performed as soon as possible, optimally within 14 days after the bleeding episode.[5,11,16,24] Total enteroscopy is possible in 70 to 90% of patients, with a diagnostic yield of 38-83%.[5,25] This device has a high positive (94-97%) and negative (83-100%) predictive value in the evaluation of GI bleeding.[24,26] In a systematic review published in 2010 CE had a pooled detection rate of 60.5% for GI bleeding.[8] It is interesting to notice that CE can be useful even in patients with acute severe bleeding.[27,28] A negative capsule assures a good prognosis, with a pooled rebleeding rate of 0.19 (95% CI, 0.14-0.25; P<0.0001).[29] A "watch-and-wait" policy with periodic clinical re-evaluation is generally acceptable after negative CE if the patient has no further bleeding and/or a significant drop in hemoglobin levels.[11,29] Significant small bowel lesions can be

missed during CE, more frequently in the proximal segments (duodenum) and cross-section imaging or device-assisted enteroscopy (DAE) should be offered to patients with persisting bleeding.[30–33] Even repetition of CE is a plausible option, since additional findings were found in up to 75% of patients with suspected small bowel bleeding, with a change in management in 62%.[34] CT enterography (CTE) should also be considered since it can have a diagnostic yield of 50-57% in patients with bleeding and negative CE.[35,36]

CE accuracy is limited by multiple factors such as transit time, peristaltic activity, bowel distension, bowel preparation, shadows, and the angle or direction of the camera.[1] So, we must always remember that CE has some major drawbacks: first there is no control in the image acquisition process; second, it has no additional diagnostic or therapeutic capabilities; third, there is a lack of specificity of some findings; fourth, the length of time required for the procedure is long, and generally the results are available in the following day; fifth, there are some contraindications, with bowel obstruction being one of it. If there is a strong suspicion of possible bowel obstruction a CT or MRI enterography should be carried out before CE. This applies to patients with established Crohn's diseases, prior radiation therapy, previous small bowel surgery and patients with symptoms suggestive of small bowel stenosis.[5]

It is important to notice that some patients have a bypass of the GI tract, has happens in Roux-en-Y anastomosis. The afferent limb is not accessible to CE and DAE is the endoscopic modality of choice to evaluate this luminal segment.[16]

In patients with a positive finding in CE a therapeutic modality must be implemented. It can be medical, endoscopic, radiological, or surgical. For therapeutic endoscopy we have push enteroscopy or DAE with the route of introduction (oral or anal) being determined by CE. DAE refers to endoscopic techniques that allow an extensive visualization of the small bowel, beyond the normal limits of push enteroscopy. It includes double balloon enteroscopy (DBE), single balloon enteroscopy and spiral enteroscopy. There is also a fourth platform, not commonly used, that is a through the scope balloon catheter. DAE is feasible as an emergent procedure in patients with ongoing bleeding, but it is more invasive than CE, not easily available, with extra resources and personnel involved, and with higher risks.[5,11] In a systematic review and meta-analysis of 10 studies DBE revealed a similar diagnostic yield to CE.[37] A more recent meta-analysis, involving 17 studies, demonstrated a diagnostic yield of 58.5% for CE and 41.5% for DBE.[38] This strength the idea that CE should be the first approach in these patients, but it is important to remember that DAE has multiple diagnostic and therapeutic capabilities.

During a long period of time intraoperative enteroscopy (IOE) was the gold standard for small bowel endoscopy. This dramatically changed with the advent of CE and DAE. IOE has diagnostic and therapeutic yields of 79.3% and 75.7%, respectively, but rebleeding may occur in up to 60% of patients and there are important morbidity and mortality.[39] For these reasons, IOE is now a last resource technique and should be considered: in patients with recurrent bleeds with multiple transfusions and hospitalizations and negative findings for all other examinations, including endoscopic and radiological; in patients with small bowel lesions not

amenable to other endoscopic or angiographic treatments (for example, when multiple bowel adhesions preclude DAE); when surgery is required for adequate resection and the lesion(s) cannot be localized during surgical exploration.[5,16,39]

Scintigraphy with red blood cells tagged with 99mTc enables the detection of bleeding at rates as low as 0.1-0.5 mL/min. However, this procedure is not easily available, has a delay of several hours until the final results are obtained, and anatomic localization of bleeding is poor.[20] 99mTc scintigraphy is probably the ideal examination for detecting slow intermittent bleeding, when other methods, namely endoscopic, have failed.[5,20]

Additionally, in younger patients with ongoing bleeding and negative evaluation with CE, CTE or other testing modalities, a diagnosis of Meckel's diverticulum should be considered. Since ectopic gastric mucosa can be seen in 10-60% of such diverticula a 99mTc-pertechnetate scan can be useful to detect this anatomic abnormality.[5,40]

Concerning treatment, it is important to remember that if a source of bleeding is identified at any given examination a specific treatment must be implemented, if feasible. Therapeutic alternatives include endoscopy (electrocautery, argon plasma coagulation, injection therapy, mechanical hemostasis), radiology and surgical alternatives. Anticoagulation and/or antiplatelet therapy should be discontinued, if possible (see specific chapter).[5] Surgery is generally a last alternative, except in some cases, such as bleeding neoplasms. It must be guided by previous examinations, and IOE can be needed during surgical intervention.

Patients with multiple small bowel angiodysplasia represent a specific group since rebleeding after endoscopic therapy is common.[41] If the patient has Heyde's syndrome (aortic stenosis and angiodysplasia) and ongoing bleeding he should be offered aortic valve replacement/repair.[5,41] In other patients, medical therapy with octreotide or thalidomide could be an alternative.[5,16,41–43]

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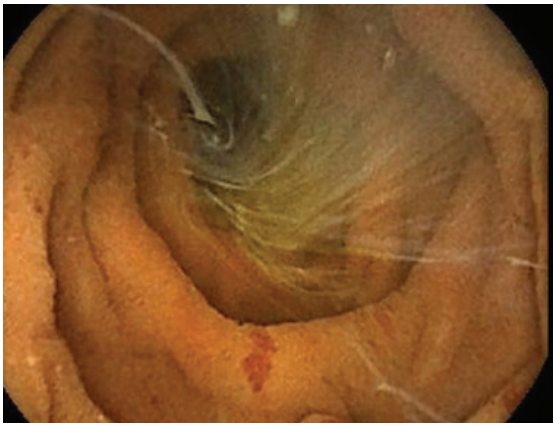

**Figure 1.** Multiple angiodysplasias in a patient with MGIB

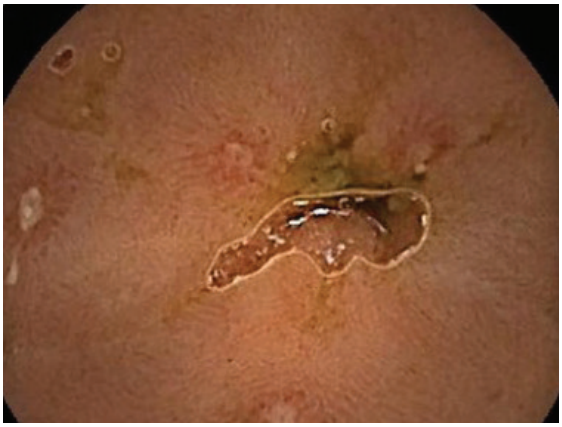

**Figure 2.** Diminutive ileal ulcers and erosions in a patient with Crohn's disease

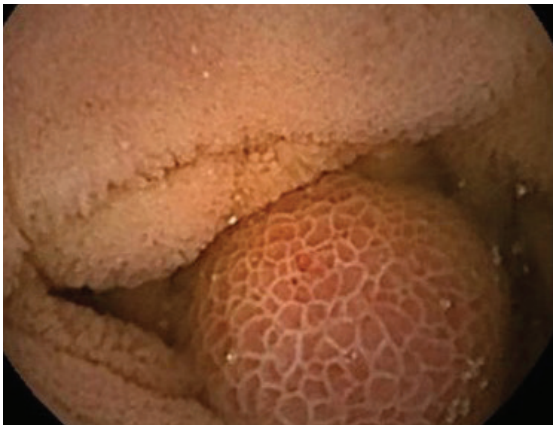

**Figure 3.** Large subepithelial lesion in the jejunum

**Overt gastrointestinal bleeding: Negative upper and lower endoscopy**

**Resuscitation and risk assessment**

**Clinical history and physical examination**
- **Assess severity**
  - Heart rate
  - Blood pressure
  - Blood tests
    - Hemoglobin
    - Prothrombin time
    - Blood urea nitrogen (BUN) and creatinine
- **Clinical history can suggest the etiology**
  - Aortic stenosis – Heyde syndrome
  - Family history of cancer at an early age – Lynch syndrome
  - Telangiectasias of lips and/or oropharynx – Rendu-Osler-Weber syndrome
  - Herpetiform dermatitis – Celiac disease
  - History of abdominal aortic aneurysm repair – aortoenteric fistula

**Hemodynamic status**

**Unstable GI bleeding or suspected active bleeding**

**Patient unstable after resuscitation**
- Fluoroscopic angiography with embolization

**Patient stable after resuscitation**
- Consider CT angiogram (CTA):
  - **If positive:**
  - Specific management:
    - Medical treatment
    - Intervention radiology
    - Device-assisted enteroscopy (DAE)
    - Surgery (with/without intraoperative enteroscopy)
  - **If negative:**
    - Consider capsule endoscopy and/or DAE

**Stable GI bleeding**
- ***No suspected bowel obstruction:*** Capsule endoscopy
  - **Positive:**
    - Specific management: Medical treatment; intervention radiology; DAE; surgery (with/without intraoperative enteroscopy)
  - **Negative:**
    - Additional bleeding – CT enterography and/or DAE and/or repeat capsule endoscopy and/or 99mTc-labeled red blood cells scintigraphy
    - No bleeding – watchful waiting
- ***Suspected bowel obstruction*** – CT/MR enterography:
  - Bowel obstruction confirmed: DAE; CT angiography
  - Bowel obstruction not confirmed: Capsule endoscopy (see above)

**Special Cases**

| | |
|---|---|
| Patients with GI tract bypass | DAE could be necessary to evaluate the excluded luminal segment |
| Suspected Meckel's diverticulum | **Consider $^{99m}$Tc-pertechnetate scan, particularly if:**<br>• Negative endoscopic examination (capsule endoscopy and/or DAE)<br>• Negative CT angiography/CT enterography |
| Heyde's syndrome | Aortic valve replacement or repair |
| Multiple small bowel angiodysplasias | • Endoscopic treatment<br>• If failure/rebleeding: consider medical treatment including octreotide or thalidomide |

CT, computerized tomography; DAE, device-assisted enteroscopy; GI, gastrointestinal

**Algorithm 3.3.** Middle gastrointestinal bleeding[5,11,16,20,28]

# Management of coagulopathy in gastrointestinal bleeding

## Anabela Rodrigues, Manuela Gomes, Carla Leal Pereira, José Aguiar

***These recommendations are not a substitute for clinician's judgment and should be used alongside other variables that may be contributing to bleeding*** [1,2]

In patients with gastrointestinal bleeding (GIB), the initial underlying pathophysiological mechanisms are the same as in any other severe hemorrhage and include loss, consumption, and dilution of coagulation factors. However, the hemostatic profile is more complex if liver disease is present.

Special attention should be paid to cases of liver disease and portal hypertension (PHT). In case of liver disease, especially if cirrhosis is present, it should be anticipated that these patients will develop a clinically significant dilutional coagulopathy and hemostatic failure, with blood loss of less than one total blood volume due to their fragile hemostatic balance.[3,4] On the other hand, mainly because of low natural anticoagulants and high factor VIII/von Willebrand factor levels, patients with cirrhosis also have an increased risk of thrombosis.[1,5,6]

In patients with acute upper GIB, restrictive transfusional therapy is recommended to avoid an increase in blood volume, particularly in cases of preexisting portal hypertension,[6] unless there is massive life-threatening hemorrhage.[7]

As in any other clinical situation, patients' initial evaluation should include the assessment of previous comorbidities and drug therapies potentially impairing hemostasis, like anticoagulants and/or antiaggregants.

It is also important to follow a multimodal, preferably viscoelastic-guided, goal-directed approach to the management of massive bleeding, ensuring hemostasis.[5,8] Coagulation factor concentrates, like fibrinogen and prothrombin complex concentrates, and other pharmacological agents play a central role in this setting.[9] For details, please refer to the coagulopathy management algorithm published elsewhere.[1]

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# 1. Massive bleeding/ transfusion

## Anabela Rodrigues

Several definitions of massive bleeding/transfusion have been published, according to the hemorrhage volume, ongoing bleeding rhythm, and number of blood transfusions.[1-6]

Definitions of massive bleeding vary and have a limited value. They include blood loss of one total blood volume (TBV) within a 24-hour period,[2-4] blood loss of more than 50% of TBV in 3 hours,[2-4] or as ongoing bleeding exceeding ≥150 mL/minute[2,3] or 1.5 mL/Kg/minute in 20 minutes. Transfusion of three units of packed red blood cells (PRBC) in one hour in gastrointestinal bleeding or four PRBC in less than four hours and hemodynamic instability roughly anticipate ongoing bleeding.[7]

This blood loss causes circulatory impairment despite resuscitation and fluid therapy (crystalloids and colloids) measures, blood transfusion, surgery, and intervention imagiology.[2]

A pragmatic clinical-based definition of massive bleeding/transfusion is 'bleeding leading to systolic blood pressure of less than 90 mmHg or heart rate of more than 110 beats per minute'.[3] In other words, this definition is provided by the combination of bleeding with a shock index (SI; heart rate/systolic blood pressure ratio) ≥1.0,[3] which refers to a hemodynamic instable patient with active bleeding. SI ≥1.0 is a marker of active bleeding, allowing to identify unstable patients.[1]

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# 2. Packed red blood cells

## Anabela Rodrigues

**Summary:**

- **In non-massive gastrointestinal hemorrhage, a restrictive strategy of red cell transfusion is recommended for many patients (Grade 1A).**[1-5]
- **Trigger: hemoglobin (Hb) <7g/dL**[5-8] **or Hb <8g/dL if heart disease is present.**[5,6]
- **Maintain target Hb of 7–9 and 8–10 g/dL in patients without and with heart disease (Grade 1A),**[1] **even during active bleeding (Grade 1C).**[8]
- **Consider transfusion of 1–2 units of packed red blood cells according to the clinical situation.**[5]
- **Continuous Hb monitoring can be used for trend monitoring (C).**[8]

Recent publications comparing more liberal (typical transfusion trigger of hemoglobin [Hb] 9–10 g/dL) with more restrictive (typical transfusion trigger of Hb 7–8 g/dL) transfusion strategies showed no difference in patient outcomes.[7] The randomized controlled trial by Villanueva *et al* in 2013, comparing liberal and restrictive red blood cell transfusion policies in patients with non-massive acute upper gastrointestinal bleeding (GIB), showed better outcome with improved 6-week survival and lower rebleeding rate in patients allocated to a restrictive red blood cell transfusion threshold of Hb <7 g/dL (post-transfusion target: Hb 7–9 g/dL).[3] Additionally, in patients with anemia, evidence from randomized controlled trials and observational studies support a restrictive blood transfusion strategy with a target Hb level of 7–9 g/dL to avoid counteracting the body's own hemostatic mechanisms of hypotension, vasoconstriction, and thrombus formation.[9] The evidence does not support increasing oxygen delivery with red blood cell transfusion when Hb is >7 g/dL, unless in patients with cardiac disease.[7]

Therefore, a Hb threshold of 7 g/dL should generally apply for red blood cell transfusions,[6,7] and a Hb target of 7–9 g/dL should apply after transfusion for patients without cardiac problems.[6,9] For patients with ischemic heart disease, the target should be the highest Hb level within this range, to prevent myocardial infarction.[9] Uncertainty remains for patients with ischemic heart disease, including acute coronary syndrome, and after cardiac surgery,[7] with higher thresholds (8 g/dL) potentially more appropriate. This threshold, as well as a Hb target of 8–10 g/dL after transfusion, are recommended by the *National Institute for Health and Care Excellence* (NICE)[6] and others.[6,7]

Erythrocytes participate in hemostasis through four mechanisms: a rheological effect (platelet margination), release of adenosine diphosphate (ADP), modulation of eicosanoid

production by platelets inducing platelet reactivity (thromboxane $A_2$), and activation of the intrinsic coagulation pathway (factors IX and X). Therefore, decreased hematocrit plays an important role in bleeding.[10]

Erythrocytes flow in the centre of the vessel and push platelets towards the endothelium, enhancing shear force and activating platelets.[10] Low hematocrit markedly decreases platelet deposition on the endothelium, irrespective of platelet count.[10] Anemia due to red cell loss has a major effect on primary hemostasis, through reduction of axial blood flow and hence reduction of platelet and plasma margination to blood vessel walls and injury sites, such that there is an inverse correlation between the hematocrit and in-vitro bleeding time.[11]

Hematocrit is known to influence hemostasis, and as a result low hematocrit is partially responsible for increased bleeding.[9,12] Erythrocytes have been shown to modulate the biochemical and functional platelet responsiveness, suggesting that they contribute to hemostasis. Two different pathways can help to explain this effect: the biochemical and the rheological effect of red blood cells on platelet margination.[9] The transfusion trigger for prophylactic platelet transfusion should consider both the hematocrit and platelet count.[9] The optimal hematocrit to sustain hemostasis in bleeding (especially uremic) patients is still unknown. This threshold hematocrit could be around 30%, but no study so far has validated this value.[9] Some chronic renal disease experts recommend correcting anemia and targeting the hematocrit to 30% to lower bleeding (Grade 1C).[13] Studies have shown that when hematocrit is >30%, bleeding time in most patients is reduced due to platelet displacement to closer to the vascular endothelium, decreasing the time required for adhesion and aggregation in response to damage.[12] The decrease in bleeding time would theoretically help prevent uremic bleeding.[12]

Restrictive therapy is recommended to avoid an increase in blood volume, especially in cases of preexisting portal hypertension.[4] In a meta-analysis, a restrictive transfusion strategy was associated with a reduction in all-cause mortality at 30 days, as well as in rebleeding, transfusion requirements, number of people requiring transfusions, and length of hospital stay.[14] No difference was found between variceal and nonvariceal subgroups.[14]

No randomized controlled trials have included participants with exsanguinating hemorrhage, in whom Hb may not be an accurate measure of blood loss.[15] Normal Hb and blood pressure values in the acute setting do not exclude life-threatening bleeding. Increased heart rate is a more sensitive early objective measure of hemodynamic status.[9] Continuous Hb monitoring can be used for trend monitoring (C).[8] In such cases, patients should be managed according to major hemorrhage guidelines.[2,5,16] Hemodynamic instability per se should not be the sole determinant of critical care admission.[15] In cases of ongoing hemodynamic instability despite adequate resuscitation efforts, activation of major hemorrhage protocol should be considered, as well as early referral to a critical care specialist to optimize circulatory management.[2,15]

Although there are no comparative studies addressing changes in coagulopathy and thrombocytopenia in GIB, it seems wise to follow a restrictive approach to the use of plasma and platelets in patients with acute upper GIB, unless there is massive life-threatening hemorrhage or evidence of severe derangements in laboratory tests.[2]

In conclusion, several randomized controlled trials and observational studies support a restrictive red blood cell transfusion strategy, with a general Hb threshold of 7 g/dL and 8 g/dL for red blood cell transfusion and a target Hb level of 7–9 g/dL and 8–10g/dL after transfusion for patients without and with cardiac disease (ischemic heart disease, including acute coronary syndrome) and after cardiac surgery, respectively.[5-7,9,15]

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# 3. Tranexamic acid

## Anabela Rodrigues

**Summary:**

**Tranexamic acid (TXA) may be considered in severe gastrointestinal bleeding (GIB) in the following cases:**[1]

- **Clinical suspicion of hyperfibrinolysis, e.g. GIB – bleeding ulcer (Grade 2A),**[2] **acute bleeding, and liver disease.**[3-5]
- **Confirmation of hyperfibrinolysis by thromboelastometry (ROTEM®):**[6-9]
  - **EXTEM ML >15%**[6-9] **or FIBTEM ML ≥10% (LI60 ≤85%).**[9]
  - **EXTEM LI30 <94%; APTEM CT <EXTEM.**[6-8]
  - **APTEM LI30 and ML better than EXTEM LI30 and ML (>25% improvement).**[6]
- **TXA - loading dose: 1g iv/10 minutes.**[2,10-12]

  **maintenance dose: 1g iv/8h in case of severe bleeding.**[13]

***[Notes:** ML: maximum lysis; LI30: lysis index at 30 minutes; CT: clotting time]*

**Overview of the use of TXA in GIB:**

- The use of TXA should be considered in non-traumatic major bleeding (Grade 1B).[14] In upper GIB, TXA was shown to reduce mortality with no associated risks, although its routine use is not generally recommended in upper and lower GIB, due to relevant doubts regarding safety and effectiveness in these indications.[5,15,16] Uncertainty about its effects on thromboembolic events is important, as many patients with acute GIB are elderly and have a high risk of thromboembolism.[15]
- Clinicians must decide whether to use TXA without strong evidence of its risk/benefit balance.[15] TXA administration should be based on clinical judgment, guided by patient history, thromboelastometry, and laboratory and radiologic investigation, tailored to treatment location, and capacity for intervention and transfusions.[17] TXA should be considered as an adjunct therapy if standard-of-care GIB treatment fails.[18]
- **Sevilla document 2013 suggests the administration of TXA in patients with bleeding peptic ulcer (Grade 2A).**[2]
- **In GIB, TXA reduces mortality, but not rebleeding (B).**[10]

Tranexamic acid (TXA) is a synthetic lysine analogue and antifibrinolytic that competitively and directly inhibits conversion of plasminogen to plasmin by blocking the lysine binding sites to the fibrin molecule.[5,12,17,19-23] TXA inhibits formation of the ternary plasminogen-fibrin (tPA complex),[23] inhibits cleavage of fibrin and degradation of the newly formed fibrin clot, finally reducing the risk of hemorrhage.[21,24] It also blocks $a_2$antiplasmin binding and inhibits inflammatory reactions.[5,19,21,25] High TXA doses inhibit complement activation[24] and partially inhibit fibrinogenolysis.[5,17,20-22] TXA has antithrombotic effect, inhibits the inflammatory effects of plasmin, and effects on platelets and factors V and VIII.[5,19] It also has a protective effect on the endothelium and a beneficial effect in modulation of inflammation and other responses following ischemia and reperfusion.[25]

TXA is an antifibrinolytic agent with a well-established role in the management of hemorrhagic shock, preventing and reducing excessive blood loss, transfusions and mortality due to trauma (especially if infusion is in less than 3 hours after injury), surgery (cardiopulmonary bypass, orthopedic and urologic surgery, among others), abnormal uterine bleeding, and postpartum hemorrhage.[18,20,21,26,27] TXA significantly increases overall survival from bleeding,[19,28,29] particularly if given as soon as possible after bleeding onset.[28,30] TXA has been widely used for prevention and treatment of hemorrhage and/or primary and secondary hyperfibrinolysis,[21] with some experts considering that it should also be used in cases of bleeding prompting transfusion.[5,21]

Antifibrinolytic drugs remain an important effective and low-cost intervention that reduces blood loss, morbidity, and mortality,[31] with no increased risk of vascular occlusive[4] or thromboembolic[32] events.

The evidence that TXA reduces bleeding and transfusion requirements in surgery and in a wide range of clinical scenarios and patient settings,[24] while also reducing trauma-associated mortality, raised the possibility that it could also be effective in gastrointestinal bleeding (GIB).[15] In fact, TXA has been used in GIB management,[29] but has not been included in the standard treatment of GIB so far.[24] Recent evidence suggests that TXA is potentially effective in GIB management,[24,33] particularly upper GIB, since it often reduces acute transfusion requirements, rebleeding, and the need for surgical intervention without increasing the risk of thrombotic events.[18]

Despite this, the rate of TXA use in upper GIB is around 0.8–1%.[18] The evidence supporting it, although not robust, suggests potential benefit.[16,18,35] However, these patients are often elderly and with several comorbidities,[24] and hence TAX dosage and thromboembolic risk should be carefully evaluated.[24]

Despite substantial evidence from randomized controlled trials (RCTs), systematic reviews, and meta-analyses of the benefit and safety of TXA in upper GIB, the utility of this agent in this setting remains unclear.[5,10-12,15,18,21,33,35-37] A Cochrane review from 2012 showed a reduction in mortality with the use of TXA versus placebo in the treatment of upper GIB.[5] However, the lack

of data regarding other outcome measures and the efficacy of TXA versus other interventions (endoscopic and proton pump inhibitor therapies) hinders the recommendation for its routine use in upper GIB.[5,21,36,37] In liver transplant surgery, meta-analyses of RCTs reported that TXA is safe and effective in reducing blood loss.[37] However, the efficacy of TXA in GIB remains controversial.[12,15,33,35,37] Currently, TXA may be considered on a case-by-case basis, particularly in patients with evidence of hyperfibrinolysis.[32,37] Some experts state that TXA should be considered as adjuvant therapy in cases of failure of standard GIB therapy.[1,5,18]

In acute upper GIB, there is evidence that high fibrinolytic activity correlates with increased bleeding.[38] Fibrinolysis may play an important role due to premature breakdown of fibrin blood clots at the bleeding site,[15] and may increase rebleeding risk.[14,15] In upper GIB, rebleeding is more closely associated with mortality, a complication in which TXA shows promise.[18] Most data about TXA in upper GIB concern peptic ulcer disease, but there are also reports of the use of this agent in this setting due to other causes.[18]

Some experts use TXA in their clinical practice in bleeding patients with laboratory evidence of hyperfibrinolysis (e.g., thromboelastography-TEG® and thromboelastometry-ROTEM®),[37] in those with cirrhosis and low fibrinogen levels (<1.5g/L) to prevent ongoing fibrinolysis,[11] and in refractory hemorrhage.[37] Doses used include a loading dose of 1 g intravenously and continuous infusion of 3 g over the next 24 hours (1 g slowly every 8 hours).[11]

**The use of TXA in upper GIB with associated liver disease was not investigated in randomized controlled trials.**[17,39,40] Liver cirrhosis increases fibrinolytic activity due to both decreased tissue plasminogen activator (tPA) clearance and decreased plasminogen activator inhibitor-1 (PAI-1) production by the liver.[40] Most cirrhotic patients are in a state of rebalanced hemostasis due to similar reductions in pro and anticoagulant proteins. This often yields a normal overall clotting tendency.[37] With worsening and advanced cirrhosis, these proteins accumulate in the blood, leading to hyperfibrinolysis in around 30–50% of patients.[37] Unfortunately, viscoelastic testing may be insensitive to this hyperfibrinolysis (e.g., endogenous tPA loses activity within minutes of blood draw).[37] Such patients may benefit from TXA.[37]

Data available so far does not allow definite conclusions on whether a truly hyperfibrinolysis state occurs in patients with chronic liver disease or whether this state is responsible for initiating and/or maintaining bleeding events.[41] Whether bleeding event in chronic liver disease patients should or not be treated with antifibrinolytics drugs is still unknown.[41] However, some consider that when liver disease patients present with fibrinolysis in combination with excessive bleeding, TXA (30 mg/Kg) should be administered under viscoelastic testing control.[4]

Bleeding events in **chronic liver disease** are not primarily due to hemostasis derangement, but instead to superimposed underlying conditions (hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction [vascular tone], renal failure, recurrent bacterial infections with subsequent development of endogenous circulating heparinoids, and disseminated intravascular coagulation), which may trigger bleeding by disrupting the unstable hemostasis balance in those frail patients.[41] Therapeutic interventions aimed at

correcting these underlying conditions are probably more effective in controlling bleeding than in correcting the hemostasis abnormalities.[41] In the context of variceal hemorrhage, over-resuscitation may aggravate bleeding by markedly increasing blood pressure within varices.[37]

A TXA loading dose of 10 mg/Kg and maintenance dose of 1 mg/Kg/hour are required to inhibit fibrinolysis.[23] Repeated doses should be used with caution in patients with renal impairment, as the drug is predominantly excreted unchanged by the kidneys.[22] Since renal impairment carries the risk of TXA accumulation, TXA dosages should be reduced according to serum creatinine levels in patients with slight-to-moderate kidney dysfunction.[21-23,29] Additionally, TXA is contraindicated in severe kidney dysfunction.[21]

**Adverse effects:** Overall, cumulative evidence shows that TXA is a well-tolerated drug.[5,17,21,42,43] According to data from a meta-analysis and Cochrane systematic review, there is currently no clinical evidence that TXA increases the risk of thromboembolic events or mortality.[23,42,43] Gastrointestinal disturbances, allergic skin reactions, and visual disturbances may occur.[5,17,23]

The most important **systematic reviews** and **meta-analyses** of TXA in patients with upper GIB are described in **Table 1.** The pooled analysis of nine RCTs of the use of TXA in upper GIB between 1973 and 2011 showed a statistically significant reduction in the risk of death in these patients.[15] However, the quality of trials included was poor. All but two trials were conducted before the widespread use of therapeutic endoscopy and proton pump inhibitors, so their results may not be applicable to current GIB patients.[15] Therefore, the effectiveness and safety of TXA in GIB is uncertain and there is currently no robust evidence to recommend its routine use in the treatment of upper or lower GIB.[15] It may be appropriate to consider it in cases of major hemorrhage, on the basis of evidence of a possible benefit and lack of harm.[32]

A search on Clinicaltrials.gov registry indicates that there are seven **ongoing double-blind RCTs focusing the use of TXA in GIB management** (mainlyupper GIB).[15,42] The main trials investigating the role of TXA in GIB are HALT-IT (*Haemorrhage Alleviation with Tranexamic Acid – Intestinal System – HALT-IT*),[14,16,44] and EXARHOSE (*Efficacy and Safety of tranexamic acid in cirrhotic patients presenting with acute UGIB*),[34,44] which included patients with acute upper and lower GIB and with significant acute UGIB plus cirrhosis, respectively.[14-16,34]

The HALT-IT trial (NCT 01658124), already completed, was an international, multicenter, randomized, double-blind, placebo-controlled trial conducted in 164 hospitals in 15 different countries.[45] Patients enrolled were aged above 16 or 18 years old (according to the minimum adult age in the respective countries) and had significant (defined as at risk of bleeding to death) upper or lower GIB. Patients received either a loading dose of 1 g TXA diluted in 100 mL of 0.9% sodium chloride over 10 minutes followed by a maintenance dose of 3 g TXA added to 1 L of any isotonic intravenous solution and infused at 125 mg/hour for 24 hours, or placebo (sodium chloride 0.9%). A total of 12,009 patients with upper and lower GIB from several causes (including liver cirrhosis in almost half of patients) were randomly allocated to receive TXA (n=5,994; 49.9%) or matching placebo (n=6,015; 50.1%). Almost half of patients had suspected

variceal bleeding due to liver disease (45% in TXA and 46% in placebo group). Study results showed that TXA did not reduce death from GIB or rebleeding, and that venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were higher in TXA than in placebo group (0.8% vs 0.4%, respectively). The risk of venous thromboembolic events was higher in patients with suspected variceal bleeding or liver disease (14 vs 2 events) than in patients with other bleeding causes (34 vs 24 events; p=0.035 for heterogeneity). The authors concluded that TXA should not be used for the treatment of GIB outside randomized trial setting. However, this study had the limitation of the timing of TXA administration over 3 hours of bleeding onset. This happens frequently due to difficulty in determining the exact time of bleeding onset and makes the contribution of increased fibrinolysis to bleeding less clear. Another limitation was the higher TXA dose and longer treatment duration (4 g over 24 hours) used in this study compared with randomized trials of TXA in trauma (2 g over 8 hours) or post-partum hemorrhage (1 g bolus with a repeat 1 g dose if bleeding persists), which resulted in no increase in the frequency of adverse events with TXA. The longer TXA treatment duration in this trial may explain the increased risk of venous thromboembolic events.[45] The authors highlighted the need for other randomized trials targeting the specific pathophysiological process of the GIB.

**Table 1. Systematic reviews and meta-analyses of tranexamic acid in patients with upper gastrointestinal bleeding**

| Author/ Year | No. RCT | No. pts | Main results | Author conclusions |
|---|---|---|---|---|
| **Bennett C *et al.* 2014,[33] UK** | 8 (19732011) | 1601 | • Less mortality in TXA group (p=0.007), but not in trials including anti-ulcer drugs or endoscopic therapy.<br>• No statically significant difference between groups in rebleeding episodes (p=0.07), blood transfusions, and risk of thromboembolic events (evaluated only in 4 trials). | • Additional high-quality RCTs are needed to determine whether TXA has a beneficial effect on serious or uncontrolled UGIB. |
| **Gluud LL *et al.* 2012,[35] Denmark** | 7 | 1654 | • TXA reduced mortality compared to placebo.<br>• No significant differences between groups on bleeding, surgery, or transfusion requirements. | • TXA cannot be recommended for routine use. |
| **Gluud LL *et al.* 2008[35]** | 7 | 1754 | • No clear effect of TXA in trials with anti-ulcer drugs or endoscopic therapy.<br>• No significant increase in the number of patients with thrombotic events in the overall TXA group. | • Additional trials/evidence of the use of TXA in combination with currently recommended interventions are required before definitive treatment recommendations can be made. |
| **Jiang M *et al.* 2016,[12] China** | 47 articles | 9528 | • PPI (iv/po) exhibited great therapeutic performance, by reducing the risk of rebleeding, all-cause mortality, need for surgery, and average hospital stay and blood transfusion amount.<br>• TXA is particularly effective in reducing the risk of rebleeding and has high performance regarding all-cause mortality and need for surgery. | • TXA is a promising medication for UGIB, as stated by other authors,[35] but further studies are needed to assess its effectiveness and tolerability. |

iv, intravenous; no, number; po, per os; PPI; proton pump inhibitor; pts, patients; RCT, randomized controlled trial; TXA, tranexamic acid; UGIB, upper gastrointestinal bleeding; UK, United Kingdom.

The EXARHOSE trial (NCT 03023189) is a multicenter, randomized, double-blind, placebo-controlled trial that will enrol 500 patients (≥18 years old) with significant acute upper GIB and cirrhosis.[34] TXA may help control bleeding by counterbalancing cirrhosis-related hyperfibrinolysis.[34,44] The aim of this study is to evaluate the efficacy of TXA in the early treatment of acute upper GIB in patients with cirrhosis (TXA used as soon as possible and within 24 hours after bleeding onset), and whether it can help reduce mortality and cirrhosis-related specific complications in the early phase of acute disease.[4]

Smith *et al*[46] conducted a prospective, double-blind, placebo-controlled RCTat a tertiary referral hospital in Australia in consecutive 100 patients aged >18 years with lower GIB requiring hospital admission from November 2011 to January 2018, who were randomly assigned (1:1) to TXA or placebo.[46] The authors concluded that TXA did not appear to decrease blood loss or improve clinical outcomes in patients presenting with lower GIB in this setting but acknowledged that a larger multicenter trial is desirable to determine the benefit of treatment with this agent.[46]

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# 4. Fibrinogen concentrate

## Manuela Gomes

**Summary:**

**Consider fibrinogen deficiency if:**[1]

- **Fibrinogen <1.5–2.0 g/L**[2-11] **and/or**
- **Blood loss ≥1.0–1.5 L and ongoing bleeding.**[2,3,10,12]
  - **Thromboelastometry (ROTEM®):**[5]
  - **FIBTEM CA5 <35MM PLUS FIBTEM CA5 <9 mm.**[13]
  - **FIBTEM CA10 <7 mm;**[4,14] **FIBTEM MCF <9 mm.**[4,6]
  - **Target: ↑FIB CA5 or CA10 >12 mm.**[4,13,14]
- **Fibrinogen concentrate: initial dose: 25–50 mg/Kg (Grade 2C).**[3,7,10,15]

*[Notes: CA5: amplitude at 5 minutes; CA10: amplitude at 10 minutes; MCF: maximum clot firmness; ↑: increase]*

Fibrinogen is produced in the liver and represents a critical coagulation factor for clot formation, acting both on secondary and primary hemostasis. It is cleaved by thrombin to produce soluble fibrin monomers that polymerize to create a net witch entraps red blood cells and platelets and forms the basis of the clot. Fibrinogen also facilitates platelet aggregation via binding of glycoprotein IIb/IIIa receptors on platelet surface. It is also an acute phase reactant and helps modulate inflammatory cellular reactions.[10]

Bleeding leads to fibrinogen loss, dilution, and consumption by clot formation, while hypothermia and acidosis impair its function. Having this is mind, maintaining a normal fibrinogen level seems to be an important therapeutic measure in coagulopathic patients. Normal plasma levels range between 1.5 and 4 g/L but can be higher in pregnancy and other clinical situations.[10,11,16]

Fibrinogen correction improves clot strength, a situation well demonstrated by viscoelastic blood testing (VET), like thrombelastography (TEG®) and rotational thromboelastometry (ROTEM®).[13] In areas like trauma and post-partum hemorrhage and in the perioperative period, an increasing number of studies support the fact that fibrinogen replacement helps to improve acquired coagulopathy and minimize the need for blood transfusion.[2,11,12] In these settings, clinical results are combined with standard coagulation tests for assessing fibrinogen levels (Clauss method) or function (TEG®/ROTEM®, the latter using FIBTEM test). Target levels are

still a matter of debate, as they seem to depend on multiple factors and clinical situations, but several guidelines, like the European Society of Anaesthesiology ones, suggest that values of <1.5 to 2.0 g/L should be corrected with fibrinogen supplementation.[3,11]

Another relevant issue is how to provide fibrinogen supplementation, with three possible options: plasma, cryoprecipitate, and fibrinogen concentrate.

Plasma is not the ideal source of fibrinogen concentrate for fibrinogen replacement. Different types of plasma are available, with mean fibrinogen levels between 2.0 and 2.9 g/L expected with solvent/detergent plasma and fresh frozen plasma (FFP; although the content may be near 1 g/L in some fresh frozen plasma units).[11] For this reason, large volumes must be administered to obtain a correction in fibrinogen levels. In addition, plasma requires ABO blood group compatibility and needs to be thawed, a process that takes time and equipment.

Cryoprecipitate has higher fibrinogen levels than FFP, although the exact value is imprecise, and contains other coagulation factors. It is usually administered as a pooled product obtained from 6 to 10 units of blood, and for this reason increases exposure of the recipient to different blood donors. But the major concern with this blood product is safety, since it is not submitted to antiviral processing. For this reason, it has been withdrawn from most European countries.[17]

Fibrinogen concentrate has the advantages of having a fixed amount of fibrinogen in a small volume (1 g per vial, possibly ranging from 0.9–1.3 g), being submitted to pasteurization and viral inactivation, being rapidly available, and not being associated with adverse thromboembolic events.[11,13,16] Fibrinogen concentrate is available in most European countries, and doses commonly recommended for hypofibrinogenemia correction in bleeding coagulopathic patients vary between 25–50 mg/Kg, depending on VET or Clauss results and situation involved. Therapy should be VET-guided whenever possible.[2,3,10,12]

In gastrointestinal bleeding (irrespective of upper, middle, or lower type), when patients have lost 1–1.5 L of blood, ongoing bleed is present, and/or fibrinogen values are <1.5–2.0 g/L, fibrinogen replacement with fibrinogen concentrate should be considered at doses of 25–50 mg/Kg, depending on VET or Clauss results and clinical situation.[1]

In this, like in other clinical situations, randomized controlled studies are needed to assess specific situations.

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# 5. Platelet transfusion

## Carla Leal Pereira

**Summary:**

**Consider thrombocytopenia and platelet dysfunction (PD) if:**[1]

- **Platelets <50x10$^9$/L**[2-9] **and persistent active bleeding.**[9-11]
- **Thromboelastometry (ROTEM®):**[11-13]
  - **EXTEM CA5 <35 mm with FIBTEM CA5 ≥9 mm.**[13]
  - **EXTEM CA10 <40mm with FIBTEM CA10 >12mm + platelets <50x10$^9$/L.**[11,12]
  - **EXT MCF <45 mm with FIB MCF >8 mm with diffuse bleeding.**[14]
- **Platelet dysfunction: liver cirrhosis Child-Pugh B/C, renal disease, antiplatelet therapy,**[7,8] **von Willebrand disease.**
- **Platelet concentrate (PC):**[15,16] **1 PC pool or 1 platelet apheresis unit per 60-70 Kg.**

*[Notes: CA5: amplitude at 5 minutes; CA10: amplitude at 10 minutes; MCF: maximum clot firmness]*

Platelet count is usually normal or reduced in liver disease. Thrombocytopenia is common and indirectly correlates with the degree of portal hypertension and hepatic decompensation. Its cause is multifactorial, involving shortened platelet survival, platelet sequestration, and/or inadequate bone marrow response.[17] While in some patients reduced platelet function may contribute to bleeding, elevated levels of von Willebrand factor (vWF) and decreased a disintegrin and metalloprotease (ADAMTS13), which limits the function of vWF on platelets in vivo, enhance platelet adhesion and may compensate for impaired platelet function and number.

Evidence from retrospective and in vitro studies showing that platelet levels in the 50.000–60.000 range promote thrombin generation made this the target of prophylactic treatment.[18] The optimal platelet count remains uncertain, although on the basis of adequate thrombin production, levels exceeding 56 x 10$^9$/L are recommended.[19]

Platelet count does not assess platelets' functional activity. Thromboelastometry (ROTEM®) also fails to assess platelet function, due to the high amount of thrombin generated during the coagulation process activated by standard reagents. On the other hand, ROTEM® Platelet system measures platelet aggregation in whole blood samples with impedance aggregometry and can be run simultaneously with thromboelastometry. Because the availability of this assay

is recent and limited to same hospitals, only few data are currently available about its laboratory and clinical value.

Current guidelines and expert opinion recommend considering platelet transfusion when active bleeding is observed in patients with platelet count below 50 x $10^9$/L. Conversely, platelet transfusion is not recommended in patients without active bleeding or hemodynamically stable (Level 5, Grade D). There is no evidence for the use of "prophylactic" platelet support to reduce the risk of rebleeding,[20] and no study addressed a ratio-based transfusion protocol in gastrointestinal bleeding (GIB). In lower GIB, there are no randomized data comparing platelet thresholds.[21] In the past, platelet transfusions were considered in non-thrombocytopenic or mildly thrombocytopenic patients with life-threatening bleeding who had been taking platelet antiaggregant drugs. However, high-quality evidence regarding the benefit of platelet transfusion is lacking, with some studies suggesting that it may be deleterious and even not supporting its use.[22] Because these specific cases can be complex, an individualized approach based on the general clinical setting is required.

Platelet concentrate (PC) pooled from 5 or 6 single donors or derived from apheresis of a single donor can be expected to increase the platelet count by 5.000–10.000 when infused. The total volume infused is approximately 250 mL of platelet-rich plasma.

The Portuguese expert group recommends the administration of one PC unit per 10 Kg of body weight or one pool of PC, or one platelet apheresis unit per 60-70 Kg (considering higher doses according to clinical situation) in cases of persistent active bleeding and platelet count below 50x$10^9$/L.[1] In this setting, it is also recommended to raise platelet count above 50x$10^9$/L prior to endoscopy. If available, ROTEM® parameters can be used as a trigger for platelet transfusion, as depicted in the proposed algorithm.

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# 6. Desmopressin

## José Aguiar, Anabela Rodrigues

**Summary:**

**Considerations in platelet dysfunction induced by acute uremic bleeding or acquired bleeding disorders:**[1]

- **Associated to renal disease (grade 2C)**[2,3] **and antiplatelet therapy (grade 2C[4]).**[4-8]
- **Platelet dysfunction is not routinely evaluated, but only by clinical decision according to renal function (creatinine clearance) and bleeding severity.**
- **Caution: Due to its antidiuretic effects, desmopressin (DDAVP) should be used with caution in pediatric and geriatric patients, to avoid fluid overload and electrolyte abnormalities (↓Na+). It should not be used in patients with type IIB or platelet-type (pseudo) von Willebrand disease, as the drug may cause platelet aggregation and thrombocytopenia.**[9,10]
- **Desmopressin (DDAVP):**[2-7,10-13] **0.3µg/Kg in 50–100 mL saline 0.9% iv over 30 minutes**[5,7,14-16] **as single dose;**[8,12] **maximum dose: 24 µg.**
- **Note: DDAVP onset of action: 15–30 minutes; pick effect: after 30–60 minutes (iv);**[12,14-18] **action lasts only 6–20 hours; loses efficacy if repeated within 12–24 hours.**[5,8,9,15,17,18]

DDAVP (1-deamino-8-D-arginine vasopressin), or desmopressin, improves dysfunctional platelet activity by increasing von Willebrand factor (vWF)-FVIII levels from endothelial stores and decreases bleeding time (BT) within approximately one hour after infusion.[12] DDAVP induces an increase in vWF, FVIII, and tissue plasminogen activator (t-PA) plasma levels, and also has vasodilatory effect.[15,19] It shortens activated partial thromboplastin time (aPTT) and bleeding time and has no effect on platelet count or aggregation, while enhancing platelet adhesion to vessel wall.[15]

DDAVP has been successfully used as a hemostatic agent in inherited (mainly vW disease-vWD type 1 and mild hemophilia A) and acquired (vWD, uremia plus renal insufficiency, liver cirrhosis, antiplatelet drugs) bleeding disorders.[13,15,19] It is not effective in vWD type 3 and in severe forms of vWD types 1 and 2,[10] and can induce transient thrombocytopenia in patients with vWD type 2B.[10] In acquired bleeding disorders, DDAVP has been mainly used in patients with active bleeding and uremia plus impaired kidney function, and also in those under antiplatelet therapy.[13,15,19] Desmopressin is the most commonly used agent in uremic patients with active bleeding (Grade 1 A) and in those who are about to undergo surgery.[12]

Doses used in this setting range from 0.3 to 0.4 µg/Kg intravenously (iv) in 50–100 mL saline 0.9% over 20–30 minutes as a single dose.[12-14,16] The total maximum dose is 24 µg. It should be noted that DDAVP has his peak effect after 30–60 minutes of iv infusion,[14,16] lasting only 6–20 hours and loosing efficacy if repeated within 12–24 hours.

In the *Essener Runde* algorithm, Lier et al proposed a multimodal therapy with DDAVP (0.3 µg/Kg iv over 30 minutes) for massive bleeding with suspicion of thrombocytopathy, with the goal of enhancing platelet adhesion plus endothelial release of vWF and FVIII, if there are alterations in Multiplate analysis.[14]

The advantage of DDAVP is its rapid onset of action, shortening the increased bleeding time in the setting of acute bleeding caused by uremic platelet dysfunction.[15] However, bleeding time tends to return to baseline within 24 hours.[12] DDAVP may be used to prevent hemorrhages in patients with liver disease and prolonged bleeding time in patients requiring invasive procedures, as liver biopsy.[15] Unfortunately, no bleeding benefits have been observed regarding variceal bleeding or liver transplant, as DDAVP is not effective in controlling acute variceal bleeding in patients with cirrhosis.[15,16]

Disadvantages of DDAVP include reported tachyphylaxis after one dose (caused by depletion of vWF from endothelial stores), fluid retention, allergic reactions with repeated use, headaches, facial flushing (face redness and warmth), hypotension, and rare thrombotic events.[9,12,13]

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# 7. Calcium chloride and magnesium sulfate

## José Aguiar, Anabela Rodrigues

**Summary:**

**Considerations in hypocalcemia and hypomagnesemia if:** [1]

- **Severe bleeding and transfusion of multiple blood components, especially in ongoing bleeding** [2,3] **and liver cirrhosis.** [4]
- **Ionized calcium ($iCa^{2+}$) <1,2** [5] **– calcium chloride** [2,]**:** 0.5–1.0g iv per 500 mL of transfused blood.[4]
- **Low magnesium (normal plasma levels 1.5–2.2 mEq/L)** [4] - **Magnesium sulfate**[4]**:** 10–15 mg/Kg with 10–20% solution over 15–20 minutes.[6]
- **Caution: Attention to induced dysrhythmias, arterial pressure fluctuations, cardiac arrest, respiratory paralysis (Mg), and central nervous system lethargy and coma.**[6]
- ***Note:*** **With iv calcium and magnesium, the onset of action and peak effect for electrolyte replacement are almost immediate.**[6]

Ionized $Ca^{2+}$ ($iCa^{2+}$) acts as a bridge between the negatively charged vitamin-K-dependent coagulation factors, phospholipids, and the endothelium.[7] Moreover, calcium protects fibrinogen from denaturation and proteolysis and influences platelet function.[7] Hemostasis is seriously impaired at values below 0.6–0.7 mmol/L.[7]

Free ionized $Ca^{2+}$, the so-called coagulation factor IV, is inversely correlated with blood pH and required for assembly of coagulation factors on the surface of platelets and injured endothelium.[8] Furthermore, $Ca^{2+}$ ions are essential, not only for fibrin polymerization and platelet function, but also for fibrinolysis and activation of the protein C system.[8]

Hypocalcemia and hypomagnesemia are often associated with massively transfused patients.[2,4,5] Their evaluation and correction are imperative[2-5] and should be accompanied by dose monitoring during infusion.

Critical values can be expected early when administering colloids and after rapid transfusion of large quantities of fresh frozen plasma,[7,8] particularly in patients with impaired liver function.[7] As citrate in blood components is primarily metabolized by the liver, this effect can be more severe in patients with cirrhosis receiving massive transfusion.[4]

In patients presenting with $iCa^{2+}$ <1.2,[5] calcium replacement (calcium chloride 0.5–1.0 g iv per 500 mL [or >2 mL/Kg/minute] of transfused blood or calcium gluconate 1–2 g iv) should be considered.[4]

Magnesium can also be affected, and low levels have unwanted side effects and should be replaced as necessary, keeping in mind that overly rapid magnesium infusion may exacerbate hypotension.[4]

Patients' central nervous, respiratory, and cardiovascular systems should be closely monitored during this electrolyte replacement.[6]

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# 8. Prothrombin complex concentrate

## Anabela Rodrigues

**Summary:**

**Considerations in deficit of other coagulation factors (thrombin formation deficit) if:**[1]

- **PT/INR or aPTT >1.5 times the normal and acute/active bleeding**[2-11] **+ acute liver failure (Grade 2C),**[12,13] **liver dysfunction.**[9,14,15]
- **Volume of blood loss: ≥150-200% (≥1.5 TBV);**[5] **<100% (<1.0 TBV) in liver disease.**[9,15]
- **Thromboelastometry (ROTEM®):**

  **EXTEM CT > 80 seconds; INTEM CT >240 seconds**[16-18] **(with EXTEM CT ≈ APTEM CT).**[17]

  **EXTEM CT > 80 seconds plus FIBTEM A5 ≥8 mm.**[19]
- **4-factor prothrombin complex concentrate (PCC):**[2,7,14,15,20] **20–30 IU/Kg.**[3,13,19]
- **Vitamin K (10–20 mg), especially if decompensated liver cirrhosis**[21]

**and/or**

- **Fresh frozen plasma (FFP):**[5,6,9,22,23] **initially 10–15 mL/Kg;**[6,8,24] **if severe bleeding, up to 20 mL/Kg.**[6,8]

**If variceal bleeding occurs, consider factor V and natural anticoagulant deficit in the following cases:** [1]

- Suspicion from underlying clinical disease and bleeding severity.
- Levels are usually low in liver disease, mainly in Child-Pugh C cirrhosis and acute liver failure.[25]
- Factor V <25% and severe acute/active bleeding.[22,23,26]
- Fresh frozen plasma (FFP):[6,22,23] up to 12 mL/Kg.
- In these situations, FFP (for low factor V level) and fibrinogen concentrate (for low fibrinogen level) can be previously associated to prothrombin complex concentrate (PCC) to improve clinical efficacy.[25]

**Note: FFP must be volume-restrictive, because fluid overload increases portal hypertension and worsens bleeding.**

Prothrombin complex concentrate (PCC) consists of 3- (without FVII) or 4-factor (F) concentrates containing non-activated coagulation factors II, VII, IX, and X, anticoagulants (protein C and S),[7,10,14,27-32] and traces of antithrombin, heparin, vitronectin,[3,27,31] and protein Z.[29,31] The half-life of the four clotting factors widely differs.[30] FII has the longest half-life (60–72 hours), and FVII the shortest (about 6 hours).[29,30] FII levels are directly proportional to thrombin generation.[29] PCC thromboembolic risk depends on both the PCC dose and patients' individual prothrombotic predisposition.[29] Several prospective clinical trials have documented that PCC contains a balanced formulation of all vitamin K-dependent procoagulant and anticoagulant proteins, with a high efficacy and safety profile.[14,15,29,30,33] PCC undergoes viral inactivation as part as the production process,[29] minimizing the potential for disease transmission.[34]

The advantages of PCC over fresh frozen plasma (FFP) include: minimal hemostasis disruption; higher speed of infusion in lower volume with higher concentration of the four clotting factors,[7,10,14,15,29,30,33] reducing the risk of fluid overload;[15] faster onset of action, prompting an international normalized ratio (INR) reduction in less than 30 minutes;[10,14,15,29,30,33] lower risk of infections and transfusion-related acute lung injury (TRALI); and no need for blood group compatibility.[10,15,29]

PCC is contraindicated in disseminated intravascular coagulation[27,31] and should be avoided in patients with suspected heparin-induced thrombocytopenia (HIT), due to the presence of trace amounts of heparin.[31] Possible PCC side effects and adverse reactions include: thromboembolic complications,[27,30,33] allergic and anaphylactic reactions,[27,30,33] fever,[27] development of inhibitors of the clotting factors present in PCC,[27] and HIT.[30,33] The risk of thromboembolic complications is low, ranging from 0.9–2%[31] to 1.4%,[30] and in most cases can be attributed to patients' underlying thrombotic risk factors.[30] No clear cause-effect relationship has been established so far.[10,29]

Several point-of-care viscoelastic tests (VET) are available and can provide an estimation of thrombin generation that can be used for goal-directed hemostatic treatment of perioperative bleeding, tailored to the individual patient according to laboratory and clinical variables, allowing to balance hemostatic benefits while minimizing prothrombotic risks.[29] The use of point-of-care testing-based transfusion algorithms including PCC and other coagulation factor concentrates enables a goal-directed and patient-tailored approach that has been shown to reduce allogeneic blood transfusion in several surgery and trauma clinical studies, with decreased thromboembolic events compared to historical controls.[4,26,29] Nevertheless, the risk of thromboembolic complications resulting from PCC treatment should be weighed against the need for rapid and effective coagulopathy correction.[4]

PCC may be therapeutically useful for acute and temporary correction of deficits of factors in prothrombin complex.[10] There are no randomized controlled clinical trials providing clinical evidence of the use of PCC, but only observational or retrospective studies[27,29] in patients with

coagulopathy, incoercible bleeding, and not treated with vitamin k anticoagulants (VKA).[10] Many of the clinical recommendations and knowledge about PCC efficacy and safety, including in gastrointestinal bleeding (GIB), emerged from these studies.

4-factor prothrombin complex concentrate (4F-PCC) is effective as adjuvant treatment and has an acceptable safety profile, not only for urgent oral anticoagulant reversal (VKA, direct oral anticoagulant - DOAC), but also for coagulopathy associated with acute major/life-threatening bleeding.[2,3,7,9,10,11,14,15,27-30,32,34-37] Integration of PCC into comprehensive coagulation algorithms for refractory bleeding is increasingly necessary.[35]

In acquired deficiency of vitamin K-dependent clotting factors, the main 4F-PCC indication is the urgent/immediate **reversal of oral anticoagulation with VKA** in adult patients with increased coagulation times (INR >1.5 or EXTEM clotting time-CT >80 seconds) and acute major/life-threatening bleeding or urgent surgery/invasive procedure (Grade 1B/2C).[2] Doses vary between 15–30 IU/Kg,[27] depending on INR values, site and extent of bleeding, and clinical situation,[27] and are safe and effective.[2,7,10,11,14,15,27-30,32,34] Coadministration of intravenous (iv) vitamin K (5–10 mg) is recommended.[7,9,29,30] PCC can also be used for **DOAC reversal** if the specific antidote is not available and in cases of severe life-threatening bleeding and/or urgent surgery/invasive procedures (dose: 25–50 IU/Kg).[36,37]

In patients with acquired prothrombin complex factor deficiency besides severe liver disease due to **loss or dilution from continuous bleeding**, PCC can be administered instead of FFP.[14,27,29] PCC administration is suggested in patients not previously treated with VKA or other oral anticoagulants, in those presenting with bleeding from trauma, perioperative hemorrhage, or acute liver failure, and when viscoelastic or coagulation tests document coagulation factor deficit (Grade 2C).[2,14,29] PCC is usually administered as second-line therapy if fibrinogen replacement and platelet transfusion fail to control bleeding.[28] A multimodal goal-directed approach is important in the management of massive bleeding,[38] and hypofibrinogenemia and thrombocytopenia correction may be prudent prior to PCC administration, to minimize the thromboembolic risk.[29] PCC administration is included in an integrated hemostatic approach incorporating bleeding clinical observation, laboratory (ROTEM®-guided) monitoring, and first-line fibrinogen concentrate therapy.[4,28,29]

A retrospective multicentre study over a 4-year period evaluated the effects of PCC – Octaplex®.[14] The most common Octaplex® use was in VKA reversal (69.2%), followed by liver dysfunction (17.3%), and uncontrolled bleeding (10.2%).[14] Octaplex® effectively and significantly reduced INR ($p < 0.0001$) and effectively reversed VKA effect in most bleeding episodes in patients with liver dysfunction.[14] No adverse drug reactions or thromboembolic events were reported.[14]

In presence of active hemorrhage, prothrombin reaches critical levels when blood loss exceeds 150–200% (³1.5 of total blood volume - TBV), revealed by prothrombin time (PT) or

activated partial thromboplastin time (aPTT) levels >1.5 times the normal and, if available, by thromboelastometry-ROTEM® (EXTEM CT >80 seconds; INTEM CT >240 seconds).[3,8,32,40] In these cases, reduced thrombin generation and need for PCC should be expected in severely bleeding patients.[32]

In cases of a trend towards elevated bleeding and prolonged clotting time despite adequate fibrinogen replacement "(fibrinogen >1.5g/L[4])", the 2013[41] and 2017[3] European guidelines and others[3,8,40] suggest PCC (20–30 IU/Kg; Grade 2C) and/or FFP (12–15 mL/Kg, up to 20 mL/Kg for severe bleeding)[8] administration to normalize EXTEM CT.[4,8] An *ex vivo* study showed that PCC was more effective than FFP in increasing thrombin generation.[15] VET-guided targeted therapy with fibrinogen and/or PCC does not seem to be associated with increased incidence of thromboembolic events.[40]

**Liver disease** is associated with decreased production of coagulation factors (vitamin K-dependent factors, fibrinogen, FV, FXIII)[9,41] and natural anticoagulants (antithrombin, protein C and S), production of dysfunctional fibrinogen (dysfibrinogenemia),[9,41] low platelet count/impaired platelet function,[15] compromised fibrinolysis, and increased FVIII/von Willebrand factor (vWF).[41] High vWF levels can partially compensate thrombocytopenia.[1,43] It should be anticipated that these patients may develop a clinically significant dilutional coagulopathy and hemostatic failure, with blood loss of less than one total blood volume (<1 TBV), due to their fragile hemostatic balance.[9,15] In addition, patients with cirrhosis also have an increased risk of thrombosis.[1,42]

PCC can also be used with favorable safety profile in patients with severe **liver disease**[9,12] **or hepatic failure,**[10,12,14,33] in those with severe bleeding or in preparation for elective surgery carrying the risk of bleeding (e.g. liver transplantation) (Grade 2C)[14,27,29,30] (dose: 20–30 IU/Kg)[43]; and when immediate hemostasis is necessary and/or the use of FFP is constrained for risk of circulatory overload.[27,44] Because vitamin K-dependent clotting factors are also decreased in liver disease, studies have suggested a potential role for PCC in patients with liver disease-related coagulopathy.[15] Due to risk of thromboembolic complications with the use of PCC (particularly when high or repeated doses are given), its administration in bleeding patients is ideally guided by VET, in addition to PT/INR, and should be preceded by adequate fibrinogen replenishment.[15,42] INR is insensitive to bleeding risk assessment in cirrhotic patients, and hence does not truly reflect coagulopathy in this setting.[41,44]

Routine coagulopathy correction may have adverse effects: transfusions may aggravate portal hypertension and the risk of esophageal and gastric variceal bleeding increases with rising portal pressure.[44] Global hemostasis assays (VET: thromboelastography-TEG® or thromboelastometry-ROTEM®) have shown normal to increased thrombin generation capability in patients with liver disease despite abnormal PT/INR, allowing to guide 4F-PCC therapy in these setting by better identifying imbalanced hemostasis.[15,41]

PCC can be less effective in controlling hemorrhagic diathesis in patients with Child-Pugh C cirrhosis and acute liver failure,[25,45] due to deficit in coagulation factors as FV (<25%)[12,26] and fibrinogen when they are not given before PCC.[25,46] PCC may be an option for selected patients with liver disease and excessive life-threatening GIB, after careful weighing risk versus benefit and after fibrinogen and FV supplementation[41] with fibrinogen concentrate and FFP (up to 12 mL/Kg), respectively, if needed.[6,25,41]

Studies[12,15,25,44,46] have shown that PCC is effective in reducing INR ($p < 0.001$) and in controlling and preventing bleeding complications,[15,44,46] and well tolerated in patients with severe (acute/chronic) liver disease with hemorrhage or before urgent surgical/invasive procedures.[15,44,46] "Very good" clinical efficacy in 76% of patients after first treatment, without evidence of thromboembolic events[15] or PCC-related adverse reactions have been reported.[12,15,25] PCC was more frequently used in patients with chronic liver disease than with acute liver failure.[15]

In a large study, Octaplex® was used in 212 GIB episodes and in patients with liver dysfunction, confirming its efficacy in most bleeding episodes.[14] In the Royal Free Hospital (London, United Kingdom), FFP has been replaced by PCC for management of liver disease coagulopathy in certain clinical settings in recent years.[15]

Evidence for the use of 4F-PCC in patients with cirrhosis has been largely limited to case series and expert opinions.[15,44,47] No randomized controlled trials have been performed to date.[47] While data is still lacking, 4F-PCC may be considered for urgent and emergency situations in cirrhotic patients,[44] particularly when there is risk of volume overload with the use of FFP (leading to portal pressure rise and variceal bleeding increase)[44] and in cases of massive bleeding.[47] The use of plasma, potentially associated with fluid overload and portal venous pressure increase, should be avoided.[1,42,43]

Based on the latest data, hepatic coagulopathy should be managed with coagulation factor concentrates rather than FFP, as they are more effective and have fewer side effects in volume overload and/or infections.[1,42] PCC administration should be VET-guided, to avoid overtreatment and thrombosis.[42]

*[Notes: PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; TBV: total blood volume; CT: clotting time; CA5: amplitude at 5 minutes].*

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# 9. Fresh frozen plasma

## Manuela Gomes

**Summary:**

**Considerations in deficit of other coagulation factors (thrombin formation deficit) if:**[1]

- **PT/INR or aPTT >1.5 times the normal and acute/active bleeding**[2-11] **+ acute liver failure (Grade 2C),**[12,13] **liver dysfunction.** [9,14,15]
- **Volume of blood loss: ≥150–200% (≥1.5 TBV);**[5] **< 100% (<1.0 TBV) in liver disease.**[9,15]
- **Thromboelastometry (ROTEM®):**

  **EXTEM CT >80 seconds; INTEM CT >240 seconds**[16-18] **(with EXTEM CT ≈ APTEM CT).**[17]

  **EXTEM CT >80 seconds plus FIBTEM A5 ≥8 mm.**[19]
- **4-factor prothrombin complex concentrate (PCC):**[2,7,14,15,20 20-30] **IU/Kg.**[3,13,19]
- **Vitamin K (10–20 mg), especially if decompensated liver cirrhosis 21**

**and/or**

- **Fresh frozen plasma (FFP):**[5,6,9,22,23] **initially 10–15 mL/Kg;**[6,8,24] **if severe bleeding, up to 20 mL/Kg.**[6,8]

**If variceal bleeding occurs, consider factor V and natural anticoagulants deficit in the following cases:** [1]

- Suspicion from underlying clinical disease and bleeding severity.
- Levels are usually low in liver disease, mainly in Child-Pugh C cirrhosis and acute liver failure.[25]
- Factor V <25% and severe acute/active bleeding.[22,23,26]
- Fresh frozen plasma (FFP): [6,22,23] up to 12 mL/Kg.
- In these situations, FFP (for low factor V level) and fibrinogen concentrate (for low fibrinogen level) can be previously associated with PCC to improve clinical efficacy.[25]

**Note: FFP must be volume-restrictive, because fluid overload increases portal hypertension and worsen bleeding.**

Fresh frozen plasma (FFP) contains several blood proteins, in particular all coagulation factors and natural anticoagulants. It was initially produced and administered for the treatment of critically wounded soldiers during the World Wars, and ever since has been increasingly used in heavily bleeding patients.[27]

Several types of plasma are marketed, but the most commonly used in Portugal is solvent detergent–treated plasma (FFP SD).

Current clinical indications for FFP transfusion mainly include the treatment of factor deficiencies when specific factor concentrates are not available, treatment of several or complex factor deficiencies, as in severe bleeding or severe hepatic disease, plasma exchange in thrombotic thrombocytopenic purpura, and reversal of warfarin and other vitamin K antagonists.[23]

In massive transfusion associated with different situations, FFP is often used in fixed ratios with red blood cells and platelet concentrate. The ratio 1:1:1 is usually associated with better outcomes. This therapeutic approach is considered by some experts as a major success, while others point out that its benefit has not been clearly established in any studies yet.[27,28]

Plasma administration has been proposed to improve integrity of the endothelium and restoration of the glycocalyx (the thick layer that coats the endothelium and acts as a protection) in patients with glycocalyx degradation due to heavy bleeding in different settings (like trauma), which is associated with poor clinical outcomes.[8,29,30]

On the other hand, it should be kept in mind that administration of FFP, as well as of other allogeneic blood products, is associated with an increased risk of morbidity and mortality.[27,28]

A recently published systematic review about therapeutic plasma transfusion in bleeding patients concluded that “although plasma is extensively used in the treatment of bleeding patients, evidence from randomized controlled trials(...)is currently lacking”.[27]

Coagulation factor loss and dilution represent the most frequent pathophysiological mechanisms in coagulopathic patients.

In presence of active gastrointestinal bleeding (GIB), prothrombin reaches a critical level (with reduced thrombin generation) when blood loss exceeds 150–200% (≥1.5 total blood volume), as evidenced by viscoelastic testing, and when prothrombin time (PT) or activated partial thromboplastin time (aPTT) is >1.5 times the normal.[3,15]

In patients with severe liver disease or hepatic failure, presence of a frail hemostatic balance is expected due to impaired synthesis of coagulation factors and natural anticoagulants. In these patients, development of a clinically significant dilutional coagulopathy and hemostatic failure with blood loss less than one blood volume (<1 total blood volume) should be anticipated.[31]

If this is the case, FFP (12–15 ml/Kg) can be considered. However, FFP single dose has been shown to have limited efficacy, and on the other hand liver disease patients may not tolerate the high FFP volume needed due to risk of circulatory overload and portal hypertension.[3,31]

In GIB associated with hepatic disease (Child-Pugh C cirrhosis and acute liver failure), coagulation factor V may reach low critical levels (<25%). In this setting, administration of FFP at a dose of 12 mL/Kg is indicated, eventually associated with fibrinogen and prothrombin complex concentrate.[25,31]

Finally, if a critical factor XIII reduction is suspected, replacement can be done with FFP (12–20 mL/Kg) if FXIII concentrate (30 IU/Kg or 1.250 IU) is not available.[3]

*[Notes: PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; TBV: total blood volume; CT: clotting time; CA5: amplitude at 5 minutes].*

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# 10. Factor XIII concentrate

## Anabela Rodrigues

**Summary:**

**Considerations in FXIII deficiency (clot instability not related to hyperfibrinolysis) if:**[1-5]

- **FXIII activity is considered to be critically reduced (<30%[6] to <60%[7]) in cases of ongoing or diffuse bleeding and low clot strength (clot instability) not related with hyperfibrinolysis and despite adequate fibrinogen concentration (Grade 2C[6]).**[2-10]
- **In cases of poor improvement of α angle and fibrinogen/fibrin polymerization after fibrinogen administration, critical FXIII reduction should be considered and corrected with FXIII replacement.**[5]
- **Thromboelastometry (ROTEM®):**

  **EXTEM ML >15% and APTEM ML >15%.**[4,8,11]

  **EXTEM CLI60 >12% + APTEM CLI60 >10% + CLI60 XIII<10%.**[12]

- **FXIII concentrate:**[4,6,7,11] **30 IU/Kg or 1.250 IU, or, if not available,**

  **Fresh frozen plasma (FFP):**[4,13,14] **12–20 mL/Kg.**

Coagulation factor XIII (FXIII) is a transglutaminase that circulates as a tetramer composed of two subunits A (FXIII-$A_2$) – intracellularly present in platelets, monocytes, and macrophages – and two subunits B (FXIII-$B_2$) – present in plasma in excess and 50% circulating as homodimer.[8,10,15] FXIII-$A_2$ becomes activated, while FXIII-$B_2$ is considered to be inhibitory, protective, and possibly regulatory.[8,10]

Subunit FXIII-$B_2$, present in plasma, is activated by the combined action of thrombin and $Ca^{2+}$.[2,15,16] FXIII function is activated by cross-linking of fibrin monomers between themselves to generate a stable fibrin strand, but also by cross-linking of fibrinogen and fibrinolysis inhibitors, like $a_2$-antiplasmin ($a_2$AP) and thrombin activatable fibrinolysis inhibitor (TAFI), to protect the fibrin clot from fibrinolysis – FXIII antifibrinolytic effect.[2,10,15,16] Thus, FXIII is crucial for maintaining hemostasis, acting on clot firmness, but mainly on clot stabilization (protecting it from fibrinolytic degradation).[10,15-17] Both the fibrinolytic system and FXIII are considered determinants of clot stabilization.[16] FXIII is essential for fibrin clot stabilization through cross-linking of fibrin monomers and increased clot resistance to fibrinolysis.[2,4,7,8,10,15] Platelet retraction, which is a prerequisite for wound healing, is dependent on FXIII.[10,15]

Fibrinogen, platelets, and FXIII are essential for clot stabilization.[18] The quality of fibrinogen/fibrin polymerization depends not only on sufficient thrombin generation and fibrinogen concentration, but also on FXIII activity.[5,8]

Decreased production and synthesis of FXIII is observed in acute hepatic failure and chronic liver disease.[10,19] A sudden quantitative reduction of FXIII measurement may compromise clot stabilization, without critically low levels of FXIII being necessarily detected.[16] FXIII levels <50% are associated with lower $a_2$AP incorporation and enhanced clot lysis.[16] FXIII deficiency is presumed to develop at late stages of blood loss.[5] A significant decrease in fibrinogen, fibrin clot strength, and a angle are detectable when FXIII decreases below 60%, but time until coagulation start is prolonged when FXIII is under 20%.[20]

Viscoelastic tests (VET), like thromboelastometry-ROTEM® or thromboelastography-TEG®, may be used as a screening test for FXIII deficiency.[21] It may show normal clotting time (CT) and low maximal clot firmness (MCF) in ROTEM®, or normal reaction time (R) and low maximum amplitude (MA) in TEG®, with evidence of fibrinolysis.[21] However, sometimes unless FXIII level is below 10–15%, TEG® or ROTEM® may be normal.[21] FXIII assay is needed to establish a diagnosis.[21] ROTEM allows assessment of FXIII deficiency in two cases: if FIBTEM MCF remains reduced even after adequate fibrinogen replacement, if EXTEM maximal lysis (ML) is >15% and APTEM ML remains >15% after tranexamic acid administration.[16] In these cases, ROTEM® can access the quality of clot formation and stabilization.[16]

Cumulative data suggests that FXIII may decrease to levels below 60-70% due to consumption in several surgical[22,23] and trauma populations, promoting increased bleeding, rebleeding, need of surgery revision and transfusion amount, besides poor outcomes.[2,3,5,7,8,10,12,17-19,22-34]

FXIII <60% is considered to have clinical significance.[18,23,25-28] FXIII plays a crucial role in maintaining hemostasis during surgery, by strengthening the fibrin clot, reducing fibrinolysis, and stabilizing the endothelial barrier.[15] In vitro and clinical studies show that minimal fibrinogen (1.5–2.0 g/L) and FXIII (>60%) levels must be maintained to minimize perioperative bleeding after major surgery or trauma.[27,28] This is accomplished through FXIII administration,[26] which is proven to decrease postoperative bleeding.[3,25-27] A correlation between decreased perioperative FXIII levels (between 28–60%, according to studies) and postoperative bleeding,[2,12,15,19,22,25,27-31] and a decrease in these complications after prophylactic FXIII administration[7,25,26] have been reported by different groups.[4,15] A significant decrease in transfusion requirements following FXIII concentrate administration has been observed in Intensive Care Unit (ICU) patients exhibiting microvascular bleeding and FXIII levels below 60%.[24,35]

Different studies suggest clinical benefits (including in clot firmness, formation, and stability[12]) with the administration of FXIII concentrate in several massive bleeding settings.[2,4,7,11,12,17,19,22,24,25,27,31,36] For this reason, some massive bleeding algorithms recommend

FXIII administration in cases of ongoing severe bleeding[12] or also clot instability nor related to hyperfibrinolysis,[11] with ROTEM®-guided evaluation in both cases: $CLI60_{EXTEM}$ >12%+ $CLI60_{APTEM}$ >10% + $CLI60_{XIII}$ <10% [12] or $ML_{EXTEM}$ >15% and $ML_{APTEM}$ >15%.[4,8,11]

Since about 50% of total FXIII is stored in platelets as $A_2$ homodimer, a decrease in platelet count would therefore entail lower FXIII availability.[15] FXIII could also attenuate hyperfibrinolysis in vitro, but only in presence of functional platelets.[15] In addition, a close correlation exists between FXIII and fibrinogen levels.[15]

There is insufficient data about the extent of blood loss required to cause critical FXIII decrease (<60%). Attention is necessary in cases of hemodilution, especially if colloids have been used, because FXIII <60% can be reached with only moderate blood loss (less than one total blood volume).[24] In case of bleeding, early diagnosis of FXIII deficiency and definition of critical FXIII levels are crucial for supplementation.[8] More randomized controlled trial are necessary to clearly evaluate the hemostatic efficacy of FXIII supplementation in different massive bleeding settings.[2,8,10]

FXIII supplementation is recommended by several updated guidelines[3,6-8] and included in coagulation support algorithms in bleeding patients with functional FXIII deficiency (ROTEM®),[8] alongside fibrinogen and prothrombin complex concentrate administration, based on the observed delayed time of coagulation initiation in VET. The use of FXIII concentrate at a level below 60% was part of the multimodal algorithms included in two recent studies in major trauma patients, resulting in substantial reductions in transfusion support requirements and improvement in clinical outcomes, including a reduction in the length of ICU stay, organ dysfunction, and hospital mortality in one study.[7,8,24] In gastrointestinal bleeding (GIB), publications are sparse and it can only be assumed that what is valid in the perioperative and trauma bleeding settings is also valid in GIB setting.

The European guidelines state that "in cases of ongoing or diffuse bleeding and low clot strength despite adequate fibrinogen concentrate, it is likely that FXIII activity is critically reduced", and "in cases of significant FXIII deficiency (e.g., <30[6] to <60%[7] activity), FXIII concentrate (*30 IU/Kg) can be administered (Grade 2C).*"[6,7] If poor improvement of α angle and fibrinogen/fibrin polymerization is observed after fibrinogen administration, a critical FXIII reduction should be considered and correction should be made through FXIII replacement.[5] In these cases, the Portuguese expert group[1] suggests replacing FXIII with fresh frozen plasma (12–20 mL/Kg)[4,13,14] if FXIII concentrate (30 IU/Kg or 1.250 IU) is not available.[4,6,7,11]

*[Notes: FXIII: coagulation factor XIII; ML: maximal lysis; CLI60: lysis index at 60 minutes after maximal clot firmness; IU: international units].*

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# 11. Recombinant activated factor VII

## Carla Leal Pereira

**Summary:**

**Persistent bleeding (uncontrolled) → rFVIIa in 'life-threatening bleeding':**[1-8]

- **Previous correction of: hyperfibrinolysis, pH, $Ca^{2+}$, temperature, fibrinogen, and platelets.**[9-11]
- **Without heparin effect (ROTEM®, VET).**[10]
- **rFVIIa concentrate:**[2,4,7,9,10,12,13] **90–120 ug/Kg iv over 2–5 minutes; a second dose may be required 2–4 hours after the first dose.**[14]

Recombinant activated factor VII (rFVIIa) was developed for use in hemophiliacs with inhibitors but has been used *off-label* in an array of life-threatening clinical conditions, such as intracerebral hemorrhage, post-partum hemorrhage, severe thrombocytopenia and massive bleeding associated with trauma, surgery, and chronic liver disease.

The general rFVIIa mechanism of action to induce hemostasis in cases of excessive bleeding associated with the above-mentioned settings relies on its capacity to generate a tight fibrin hemostatic plug through increased thrombin generation at the injury site.[15] The literature describes two potential mechanisms mainly occurring on two types of surfaces. At pharmacological doses, rFVIIa is thought to bind and form complexes with tissue factor (TF) released from extravascular spaces at the vascular disruption sites, and the resulting TF-rFVIIa complex activate the coagulation pathway via activated factor X in combination with activated factor V. Alternatively, rFVIIa may directly bind to activated platelets, which concentrate factor X activation at vascular injury sites.[16]

A hemostatic agent as rFVIIa is a potential weapon in the prevention and interruption of bleeding in patients with end-stage liver disease, even if the main bleeding cause is not hemostasis defects but rather hemodynamic alterations of portal hypertension, endothelial dysfunction, and renal failure.[17]

rFVIIa has been mostly studied in cirrhosis and variceal bleeding.[18] In an open-label study including 10 consecutive patients with alcoholic cirrhosis (Child-Pugh classes B and C) and bleeding from esophageal varices, the prolonged prothrombin time was corrected,

and prompt bleeding control was achieved in all patients.[19] The European Study Group of rFVIIa in upper gastrointestinal hemorrhage published the results of a randomized, double-blind study carried out in 245 cirrhotics randomized to receive rFVIIa or placebo in addition to standard pharmacological and endoscopic treatment.[20] No significant differences were found in the study's primary composite endpoint (death and failure to control bleeding and rebleeding). However, in a secondary data analysis, rFVIIa reduced variceal bleeding in the subgroup of patients with severe cirrhosis (Child-Pugh classes B and C). The latter finding prompted the same investigators to carry out another randomized clinical trial in patients with more severe liver disease.[21] A total of 256 patients with severe cirrhosis and variceal bleeding were evaluated, and again no significant effect of rFVIIa was observed in the primary composite endpoint of 24-hour arrest of bleeding and 5-day rebleeding or death.[21] Adverse events, including thromboembolic complications, were comparable between study groups. A more recent meta-analysis found no evidence that rFVIIa reduced the risk of death in patients with severe liver disease and upper gastrointestinal bleeding. [22]

The meta-analysis by *Bendtsen et al.* showed a beneficial effect of rFVIIa on the primary composite endpoint of control of acute bleeding, prevention of rebleeding on days 1–5, and 5-day mortality, in patients with advanced cirrhosis (Child-Pugh score >8) and active bleeding from esophageal varices at endoscopy.[23] This agent may be used as rescue treatment in patients with uncontrolled bleeding after standard treatment.[23]

Current evidence suggests that rFVIIa is both safe and effective, both in hemophilic and non-hemophilic setting. The product's safety is likely to be due to its selective location at the bleeding site. Many of the thrombotic events occurred in patients with predisposition to thrombotic complications, such as diabetes mellitus, obesity, cancer, and atherosclerotic cardiovascular disease, highlighting that their approach should be made with caution.[24]

In conclusion, apart from its marginal efficacy in the treatment of variceal bleeding, the costs and adverse events of rFVIIa administration and absence of significant survival benefits should not be neglected.[25]

According to the U.K. guidelines for control of active variceal hemorrhage in cirrhosis, there is insufficient evidence to recommend the use of rFVIIa in acute variceal hemorrhage (Level 1b, Grade B).[26] The latest European Society of Anesthesiology guidelines suggest that off-label administration of rFVIIa can be considered in life-threatening bleeding which cannot be stopped by conventional, surgical, or interventional radiological means and/or when comprehensive coagulation fails (Grade 2C).[9] According to these guidelines, rFVIIa should only be considered alongside ph correction (Grade 1C).[9]

As the evidence so far has not shown a clear benefit with this agent, further larger randomized controlled trials are needed to define its role and assess its safety in this setting.

The Portuguese expert group recommends considering the administration of rFVIIa (90–120 µg/Kg) as rescue treatment in cases of uncontrolled persistent or life-threatening bleeding, and after correction of acidosis, hypocalcemia, hypothermia, fibrinogen levels, thrombocytopenia, and hyperfibrinolysis for clot formation improvement.[1]

*[Notes: rFVIIa: activated recombinant factor VII; $Ca^{2+:}$ calcium; ROTEM®: thromboelastometry; VET: viscoelastic testing; iv: intravenous].*

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**Massive bleeding/transfusion**[6,14,27]

- ***Blood loss:***[6] 1 TBV/24 h or >50% of the TBV/3 h
- ***Transfusion:*** GIB – 3 PRBC/1 h; 4 PRBC in <4 h and hemodynamic instability, ± anticipated ongoing bleeding;[14] ≥10 PRBC/24 h
- ***Ongoing bleeding:*** 150 mL/min;[6] 1.5mL/Kg/min in 20 min
- **PLUS CIRCULATORY INSUFFICIENCY BESIDES ALL RESUSCITATION**

*Bleeding persists, despite control of previous conditions?*

**PRBC- Trigger:**
**Hb <7 g/dL;[6,28,29] < 8 g/dL if heart disease**[28]
- In non-massive GIB, a restrictive strategy of RBC transfusion is recommended (Grade 1A)[27,30]

*Yes* →

**PRBC**
1-2 PRBC units according to clinical situation
Continuous Hb monitoring can be used as "trend" monitoring (Evidence C)[9]

*Yes* →

**Maintain target: Hb: 7–9 g/dL[6,28,29] and 8–10 g/dL**[28]
In patients with and without heart disease (Grade 1A), even during active bleeding (Grade 1C)[9]

**Consider HF**
- Clinical suspicion of HF, e.g., GIB – bleeding ulcer (Grade 2A),[30] acute bleeding and LD[31,32]
- ***Confirmation of HF[11,33] -ROTEM:***
- EXTEM ML ≥15%[11,33,34] or FIBTEM ML ≥10% (LI60 ≤85%)[34];
- EXTEM LI30 <94%; APTEM CT < EXTEM CT[11,33]
- APTEM LI30 and ML better than in EXTEM LI30 and ML (>25% improvement)

*Yes* →

**TXA**[9,30]
- Loading dose: 1 g iv/10 min;
- Maintenance: 1 g iv/8 h if severe bleeding[14]

***In GIB, TXA reduces mortality but not re-bleeding***[9]

**Consider fibrinogen deficiency**
- Fibrinogen <1.5-2.0 g/L[7,9,11,27,30,35] and/or
- Blood loss ≥1.0-1.5 L and ongoing bleeding[7,9,30]
- ROTEM:
- EXTEM A5 <35 mm + FIBTEM A5 <9 mm[32,34]
- FIBTEM CA10 <7 mm[11,33]; FIBTEM MCF <9 mm[11]
- Target: ÐFIBTEM CA5 or CA10 ≥12 mm[11,33,34]

*Yes* →

**FC**
Initial dose: 25–50 mg/Kg
(Grade 2C)[7,9,35]

**Consider thrombocytopenia/Platelet dysfunction (PD)**
- Platelets <50x10$^9$/L[5,6,27,29,35] and persistent active bleeding[9,11,29]
- ROTEM:[11,33,34]
- EXTEM A5 <35mm + FIBTEM A5 ≥9mm[34];
- EXTEM CA10 <40mm with FIBTEM CA10 > 12mm+P<50x10$^9$/L[11,33]
- EXTEM MCF <45 mm with FIBTEM MCF >8 mm with diffuse bleeding
- **PD:** Liver cirrhosis Child-Pugh B/C, renal disease, APT, vWD,

*Yes* →

**Platelet concentrate (PC)**[35]
1 PC pool or 1 platelet apheresis unit per 60–70 Kg

**Acute uremic bleeding or acquired bleeding disorders with induced PD**
- Associated to renal disease (Grade 2C),[9] APT (Grade 2C)[35]
- PD usually not evaluated. Only by clinical decision according to renal function (CrCl) and bleeding severity
- Caution: Pediatric/geriatric patients, because of its antidiuretic effects, to avoid fluid overload and electrolyte abnormalities (↓Na+)

*Yes* →

**Desmopressin (DDAVP)**[9,30,35]
0.3 µg/Kg/50-100 mL saline 0.9%, iv, over 30 min[36,37] as a single dose; Maximum dose: 24 µg
**Note:** DDAVP: Pick effect after 30–60 min (iv);[36,37] lasting only 6-8 h; Loose efficacy if repeated within 12–24 h

**Consider hypocalcemia/hypomagnesemia**
- If severe bleeding and multiple blood components were transfused, especially in ongoing bleeding[35] and liver cirrhosis[5]
- If ionized calcium (iCa+) <1.2;[14] if magnesium is low[5]

*Yes* →

**Calcium Chloride**[5]
0.5–1.0 g iv per 500 mL of transfused blood

*Yes* →

**Magnesium sulfate**[5]

**Consider deficit of other CF (thrombin formation deficit)**
- TP/INR or aPTT >1.5 x normal and acute/ active bleeding[5,7,9,28,30,32] + acute liver failure (ALF) (Grade 2C),[35,38] LD[35,39,40]
- Volume blood loss: ≥ 150–200% (≥1.5 TBV)[7,35] < 100% (<1.0 TBV) in liver disease[39]

ROTEM:
- EXTEM CT > 80 s; INTEM CT >240 s[11,33] with EXTEM CT ≈ APT CT[11]
- EXTEM CT > 80 s + FIBTEM A5 ≥8 mm[34];

*Yes* →

**Prothrombin complex concentrate (PCC)**[5,30,32,39]
20–30 IU/Kg[9,35,34]
**Vitamin K** [4] (10–20 mg)
If deficiency, especially if decompensated liver cirrhosis
**or/and**
**Fresh frozen plasma (FFP)**[27]
Initially 10–15mL/Kg;[7,27,34] If severe bleeding: up to 20 mL/Kg[7,27]
**Note:** Must be volume-restrictive, because fluid overload increases portal hypertension/worsens bleeding

*If Variceal Bleeding* ↓

**Consider FV and natural anticoagulant deficit**
- Suspicion by underlying clinical disease and bleeding severity
- Levels are usually low in LD, mainly in cirrhosis Child-Pugh C and ALF[40]
- FV <25% and severe acute/active bleeding[41]

*Yes* →

**FFP**[27]
up to 12 mL/Kg
In these situations, FFP (↓FV) and FC (↓Fib.) can be associated to PCC to improve clinical efficacy[40]
**Note:** Must be volume-restrictive, because fluid overload increases portal hypertension/worsens bleeding

*Bleeding persists, despite control of the above conditions?*

*For all types of gastrointestinal bleeding* ↓

*Yes* →

**Consider FXIII deficit (clot instability not related to HF)**
- Consider that FXIII activity is likely to be critically reduced (<30%[9] to <60%[41]) in cases of ongoing or diffuse bleeding and low clot strength (clot instability) not related with HF and despite adequate fib. concentration (Grade 2C[9])[7,9,41,42]
- If poor improvement of α angle and fib./fibrin polymerization after fib. administration, a critical reduction in FXIII should be considered and corrected by substituting FXIII[42]
- ROTEM: EXTEM ML >15% and APTEM ML >15%[7,11]

EXTEM CLI60 >12% + APTEM CLI60>10% + CLI60 XIII <10%[36]

**FFP**[7]
12–20 mL/Kg
**or**
**FXIII concentrate**[7,9,11,41]
30 IU/Kg or 1.250 IU

*Yes* →

*Bleeding persists, despite control of the above conditions?*

**Persistent bleeding (uncontrollable)? → rFVIIa**
***"Life-threatening bleeding"***[5-7,30]
- Previously correct: HF, pH, $Ca^{2+}$, temperature, fibrinogen and platelets[9,11]
- Without heparin effect (ROTEM, VET)

*Yes* →

**rFVIIa**[7,9,30]
90–120 mg/Kg, iv, over 2–5 min
*2nd dose may be required 2–4 h after the 1st dose*[8]

*Very severe coagulopathy since the beginning or at any point?*

**SEVERE CLOT DEFICIENCY**[11,33]
***Consider Severe Coagulopathy:***
- Active/severe bleeding
- ROTEM: EXTEM CA10 < 30mm

*Treat immediatly* →

**TXA:** 1 g/10 min (15–20 mg/Kg)[11,33]
**FC:** 25–50 mg/Kg (6–8 g)[11,33]
**PCC:** 20–30 IU/Kg[11,33]
**PC:** 1 PC pool or 1 platelet apheresis unit/ 60-70Kg[11,33]

Notes:
- Depending on bleeding severity, concomitant administration of some of these products may be necessary, as well as repeated doses.
- Although rare, the referred treatment order can be changed, depending on the specific clinical situation.
- If possible, coagulation assessment should be performed after each specific treatment episode.

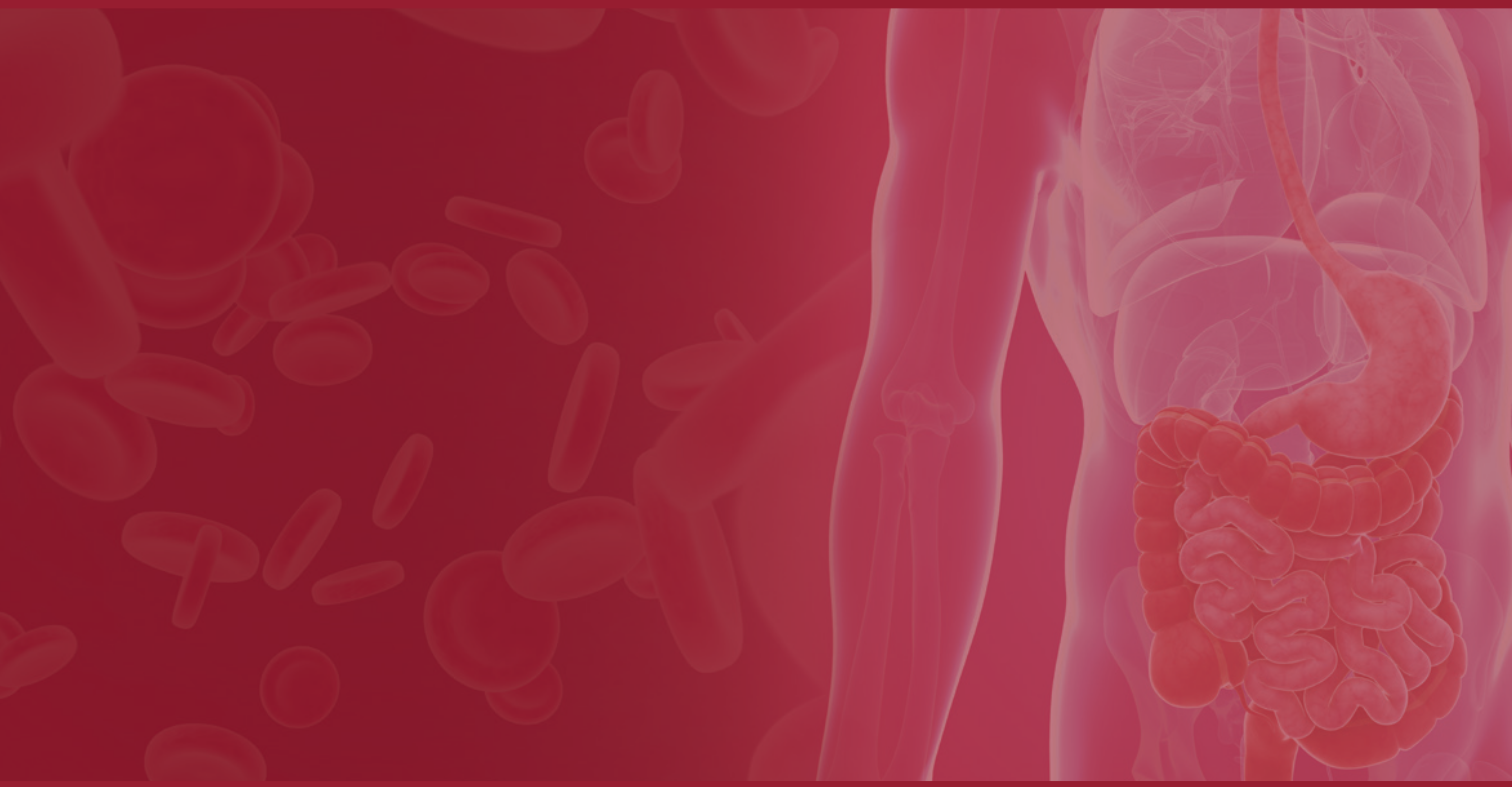
ALF, acute liver failure; aPTT, activated partial thromboplastin time; $Ca^{++}$, calcium; CF, coagulation factor; CrCl, creatinine clearance; F, factor; FC, fibrinogen concentrate; Fib, fibrinogen; HF, hyperfibrinolysis; GIB, gastrointestinal bleeding; h, hour; Hb, hemoglobin; INR, international normalized ratio; iv, intravenous; LD, liver disease; min, minute; mL, milliliter; $Na^{+}$, sodium; APT, antiaggregant platelet therapy; PD, platelet dysfunction; PRBC, packed red blood cell; PT, prothrombin time; RBC, red blood cell; TBV, total blood volume; VET, viscoelastic test; VWD, von Willebrand disease

**Algorithm 4.** Coagulopathy management in gastrointestinal bleeding

# GLOSSÁRIO

**ABCDE,** Airway, Breathing, Circulation, Disability, Exposure
**ABG**, arterial blood gas
**ACLF,** acute-on-chronic liver failure
**ACS,** acute coronary syndrome
**ADP,** adenosine diphosphate
**AF,** atrial fibrillation
**ALF**, acute liver failure
**Alg**, algorithm
**ALT**, alanine aminotransferase
**APT**, antiaggregant platelet therapy
**APTEM,** activation as in EXTEM with the addition of aprotinin or tranexamic acid, fibrinolysis inhibitors
**aPTT**, activated partial thromboplastin time
**AST,** aspartate aminotransferase
**AUGIB,** acute upper gastrointestinal bleeding
**BMS**, bare metal stent
**BP**, blood pressure
**BRS,** bioresorbable stent
**BT,** bleeding time
**BUN,** blood urea nitrogen
**$Ca^{++}$,** calcium
**CA10,** amplitude at 10 minutes
**CA5,** amplitude at 5 minutes
**CAD,** coronary artery disease
**cAMP,** cyclic adenosine monophosphate
**CE,** capsule endoscopy
**CF,** coagulation factor
**CFC,** coagulation factor concentrate
**C-FIIa**, chromogenic anti-FIIa assay
**cGMP,** cyclic guanosine monophosphate
**CLD,** chronic liver disease
**CLI60,** Lysis index at 60 minutes after maximal clot firmness
**$CO_2$**, carbon dioxide
**COX,** cyclooxygenase
**CrCl,** creatinine clearance
**CRP,** C-reactive protein
**CT,** clotting time
**CT,** computerized tomography
**CTA,** computerized tomography angiography
**CTE,** computerized tomography enterography
**CVC,** central venous catheter
**CVP,** central venous pressure
**CXR,** chest X-ray
**DAE,** device-assisted enteroscopy
**DAPT,** double antiplatelet therapy
**DBE,** double balloon enteroscopy
**DDAVP,** desmopressin/1-deamino-8-D-arginine vasopressin
**DES,** drug-eluting stent
**DOAC,** direct oral anticoagulant
**DTI,** direct thrombin inhibitor
**dTT,** diluted thrombin time
**ECA,** ecarin chromogenic assay
**ECG,** electrocardiogram
**ECT,** ecarin clotting time
**EMA,** European Medicines Agency
**ESC,** European Society of Cardiology
**ESGE,** European Society of Gastrointestinal Endoscopy
**EXTEM,** activation of clot formation by thromboplastin
**F,** factor
**FBC,** full blood count
**FC,** fibrinogen concentrate
**FDA,** U.S. Food and Drug Administration
**FEIBA,** factor eight inhibitor bypass activity
**FFP,** fresh frozen plasma
**Fib,** fibrinogen
**FIBTEM,** activation as in EXTEM with the addition of cytochalasin D, a platelet blocking substance
**FV,** coagulation factor V
**FVIII,** coagulation factor VIII
**FXIII**, coagulation factor XIII
**GBS,** Glasgow-Blatchford Score
**GI,** gastrointestinal
**GIB,** gastrointestinal bleeding
**GOV1,** gastroesophageal varices type 1
**GOV2,** gastroesophageal varices type 2
**GP,** glycoprotein
**h**, hour
**Hb,** hemoglobin
**Hep,** heparin
**HF,** hyperfibrinolysis
**HIT,** heparin-induced thrombocytopenia
**HR,** heart rate
**hs-cTnI,** high-sensitivity cardiac troponin
**Htc,** hematocrit
**HTPR,** high on-treatment platelet reactivity
**iCa+,** ionized calcium
**ICU,** Intensive Care Unit
**INR,** international normalized ratio
**INTEM,** activation of clot formation via the contact phase
**IOE,** intraoperative enteroscopy

**P2Y12i,** P2Y12 inhibitor
**IU,** international unit
**IV,** intravenous
**LC-MS,** liquid chromatography - mass spectrometry
**LD,** liver disease
**LGI,** lower gastrointestinal
**LGIB,** lower gastrointestinal bleeding
**LI30,** lysis index at 30 minutes
**LMWH,** low-molecular-weight heparin
**LOS,** length of stay
**m,** minute
**MACE,** major adverse cardiovascular event
**MAP,** median arterial pressure
**MBP,** mean blood pressure
**MCF,** maximum clot firmness
**MELD,** model for end-stage liver disease
**MGIB,** middle gastrointestinal bleeding
**ML,** maximum lysis
**ml,** milliliter
**MNPT,** mean normal prothrombin time
**MRI,** magnetic resonance imaging
**Na+**, sodium
**NICE,** National Institute for Health and Care Excellence
**NSAID,** nonsteroidal anti-inflammatory drug
**NV,** normal value
**NVAF,** non-valvular atrial fibrillation
**$O_2$,** oxygen
**OAC,** oral anticoagulant
**OTSC,** over-the-scope clip
**PAI-1**, plasminogen activator inhibitor-1
**$PaO_2$,** partial pressure of oxygen
**PC,** platelet concentrate
**PCC,** prothrombin complex concentrate
**PCI,** percutaneous coronary intervention
**PD,** platelet dysfunction
**PGi2,** prostaglandins
**PHT,** portal hypertension
**po**, per os
**PPI,** proton pump inhibitor
**PRBC,** packed red blood cell
**PT,** prothrombin time
**pt**, patient
**PTT,** pre-transfusional test
**PVC,** premature ventricular contraction
**RBC,** red blood cell
**RCT,** randomized clinical trial
**rFVIIa,** activated recombinant factor VII
**RGD,** arginine-glycine-aspartic acid
**$SaO_2$,** oxygen saturation
**SB,** Sengstaken-Blakemore
**SBP,** systolic blood pressure
**SI,** shock index
**SIHD,** stable ischemic heart disease
**$SvO_2$,** saturation of central venous oxygen
**TAFI,** thrombin activatable fibrinolysis inhibitor
**TBV,** total blood volume
**TF,** tissue factor
**TIPS,** transjugular intrahepatic portosystemic shunt
**TM,** transfusion medicine
**tPA,** tissue plasminogen activator
**TRALI,** transfusion-related acute lung injury
**TT,** thrombin time
**TTS,** through-the-scope clip
**TXA,** tranexamic acid
**TxA2,** thromboxane A2
**U,** unit
**UFH,** unfractionated heparin
**UGI,** upper gastrointestinal
**UGIB,** upper gastrointestinal bleeding
**UK,** United Kingdoom
**VET,** viscoelastic test
**VKA,** vitamin K antagonist
**VTE,** venous tromboembolism
**VWD,** von Willebrand disease
**VWF,** von Willebrand factor



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