

# PROPOSAL OF A CLINICAL CARE PATHWAY FOR THE MANAGEMENT OF ACUTE UPPER GASTROINTESTINAL BLEEDING

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**ABSTRACT - Background** - Upper gastrointestinal bleeding implies significant clinical and economic repercussions. The correct establishment of the latest therapies for the upper gastrointestinal bleeding is associated with reduced in-hospital mortality. The use of clinical pathways for the upper gastrointestinal bleeding is associated with shorter hospital stay and lower hospital costs. **Objective** - The primary objective is the development of a clinical care pathway for the management of patients with upper gastrointestinal bleeding, to be used in tertiary hospital. **Methods** - It was conducted an extensive literature review on the management of upper gastrointestinal bleeding, contained in the primary and secondary information sources. **Results** - The result is a clinical care pathway for the upper gastrointestinal bleeding in patients with evidence of recent bleeding, diagnosed by melena or hematemesis in the last 12 hours, who are admitted in the emergency rooms and intensive care units of tertiary hospitals. In this compact and understandable pathway, it is well demonstrated the management since the admission, with definition of the inclusion and exclusion criteria, passing through the initial clinical treatment, posterior guidance for endoscopic therapy, and referral to rescue therapies in cases of persistent or rebleeding. It was also included the care that must be taken before hospital discharge for all patients who recover from an episode of bleeding. **Conclusion** - The introduction of a clinical care pathway for patients with upper gastrointestinal bleeding may contribute to standardization of medical practices, decrease in waiting time for medications and services, length of hospital stay and costs.

**HEADINGS** - Gastrointestinal hemorrhage. Hematemesis. Melena. Endoscopy. Critical pathways. Clinical protocols.

## INTRODUCTION

Upper gastrointestinal bleeding (UGB) is defined as the intraluminal bleeding proximal to the Treitz ligament<sup>(14)</sup>. Regarding the etiology, can be classified as nonvariceal and variceal UGB. Hematemesis and melena are signs and/or symptoms of UGB. The cause of UGB may be established in approximately 80% of cases, and the most frequent diagnoses are peptic ulcers (37%-55%), gastroduodenal erosions (6%-24%), esophageal varices (10%-23%), esophagitis (4%-6%)<sup>(14)</sup>.

UGB is the most common emergency in Gastroenterology, with significant clinical and economic implications. It presents incidence of 0,7 to 1,5 cases every 1,000 inhabitants of the general population, annually, in the United States of America (USA). It is cause of 250,000 to 300,000 hospitalizations each year, and estimated total spending at more than 2.5 billion dollars per year, by the American health care system<sup>(43)</sup>. Mortality is 3.5 to 10% in cases of non-variceal UGB<sup>(31)</sup>, and 15% to 20% in 6 weeks after

variceal UGB, but it may reach 30% in patients with advanced cirrhosis<sup>(26)</sup>.

Brazil data on UGB are not known, but is expected to be comparable to global statistics. In addition, the low socioeconomic condition is associated with increased incidence of UGB<sup>(12)</sup>.

The correct establishment of support measures and specific therapy for the UGB is associated with decreased mortality. Study demonstrated reduction of up to 28% on in-hospital mortality with the use of the latest therapies on variceal UGB<sup>(15)</sup>.

Clinical pathways in urgent and emergency services are extensively used guides, which aim to provide a simplified view to the diagnostic and therapeutic approach of frequent and relevant diseases of daily medical practice. For these characteristics, the critical use of clinical pathways is an important tool for physicians, especially for those under training, because it enables simplified, standardized and effective service.

Meta-analysis performed by Rotter et al.<sup>(45)</sup> has shown that the use of clinical pathways, in different clinical or surgical situations, was associated with

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shorter hospital stay and lower hospital costs. With regard specifically to the treatment of UGB, studies have shown reduced cost and length of hospital stay after introduction and use of clinical pathways<sup>(37, 43)</sup>.

**OBJECTIVE**

The objective of this study was the development of a clinical care pathway for patients with UGB, who are assisted at the emergency rooms and intensive care units (ICUs) of tertiary hospitals. This clinical pathway was originally designed to be used at the University Hospital of Federal University of São Paulo.

**METHODS**

For the development of an updated clinical pathway, we conducted an extensive review about the management of UGB. Initially with the analysis of the latest consensus opinion of experts, contained both in national and international databases, and then the data contained in the secondary information sources like Cochrane Review, UptoDate, Dynamed, ACP Journal Club and Evidence Based Medicine. Subsequently, we searched for evidences in the primary information sources of SciELO, Medline, Lilacs and Embase.

We use a structured way to elaborate a question, that is synthesized by the acronym P.I.C.O., where P corresponds to the patient or population, I of intervention or indicator, C for control or comparison, and O of outcome<sup>(10)</sup>. From the structured question, we identified the keywords in the Virtual Health Library and the MeSH Database. Finally, the keywords were organized for research with the addition of the booleans AND, OR or NOT.

Articles were selected initially from the title, and its relevance was then confirmed by the review of the corresponding abstract. We excluded publications with content that was considered irrelevant. Additional articles were identified by manual search of references lists of selected articles.

Only the class I and II recommendations were included for the development of this clinical pathway, in accordance with the classification of recommendations and levels of evidence of the American College of Cardiology Foundation and the American Heart Association Practice Guidelines<sup>(4)</sup>(Figure 1).

This study was approved by the Ethics and Research Committee, from Federal University of São Paulo (#115.913).

**LITERATURE REVIEW**

**Initial assessment**

The evaluation of patients with suspected UGB must contain data about the current and past medical histories, physical examination and laboratory tests. The objectives are to early assess the severity of bleeding, identify a possible etiology, and provide initial therapy.

Blood tests with complete blood count, coagulation profile, electrolytes (sodium, potassium), urea and creatinine

Grade of recommendation	
Class I	There is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	There is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful
Level of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized clinical trial, or nonrandomized studies
Level C	Consensus opinion of experts, cases studies, or standard of care

FIGURE 1. Classification of recommendations and levels of evidence

must be requested on admission. The blood typing should also be ordered by the possibility of blood transfusions<sup>(14)</sup>.

**Risk stratification**

Risk stratification of cases with UGB enables to identify the high-risk group with increased chance for worse outcomes, and also may select the low-risk group that can be discharged early. For that, it is used prognostic scales take into consideration clinical, endoscopic, and laboratory findings<sup>(13, 44)</sup>.

The Rockall score (RS) was primarily developed for assessment of mortality after 30 days of UGB (Figure 2). Rebleeding and mortality directly increase with the value of the RS<sup>(44)</sup>.

Patients with total RS ≤2 are considered low-risk, and can receive early hospital discharge. The clinical RS (pre-endoscopic) equal to zero identifies about 15% of cases. These patients can be submitted to outpatient endoscopy, given the mortality and rebleeding low risks<sup>(44)</sup>.

Glasgow Blatchford score (GBS) was developed to predict mortality and medical intervention (blood transfusion, endoscopic or surgical treatment) after UGB episode<sup>(13)</sup>. The GBS only takes into account laboratory tests and clinical findings to its calculation, and can be easily used prior endoscopy (Table 1).

Patients with GBS ≥1 are considered high-risk for medical intervention and mortality, with >99% sensitivity. On the other hand, patients with EGB=0 are considered low-risk, and therefore can be early discharged, with subsequent outpatient endoscopy<sup>(42)</sup>.

	0	1	2	3	
Age	<60	60-79	≥80	-	
Shock (Pulse: bpm, SBP: mmHg)	Pulse <100 SBP ≥100	Pulse ≥100 SBP ≥100	SBP <100	-	
Comorbidities	No major comorbidities	-	CF, IHD, any major comorbidity	RF, LF, disseminated malignancy	Clinical score
Diagnosis	Mallory-Weiss tear, no lesion identified and no SRH	All other diagnoses	Malignancy of upper GI tract		
Major SRH	None or dark spot only	-	Blood in the upper GI tract, adherent clot, visible or spurting vessel		Additional criteria for total score

FIGURE 2. Rockall score

SBP: systolic blood pressure; CF: cardiac failure; IHD: ischemic heart disease; RF: renal failure; LF: liver failure; SRH: stigmata of recent hemorrhage; GI: gastrointestinal.

TABLE 1. Glasgow blatchford score

Risk factors	Findings	Score
Urea (mg/dL)	≥39 and <48	2
	≥48 and <60	3
	≥60 and <150	4
	≥150	6
Hemoglobin (g/dL)	Men ≥12 and <13	1
	Men ≥10 and <12	3
	Women ≥10 and <12	1
	Men or Women <10	6
Systolic blood pressure (mmHg)	100-109	1
	90-99	2
	<90	3
Pulse ≥100 bpm		1
Presentation with melena		1
Presenting with syncope		2
Hepatic disease		2
Cardiac failure		2

TABLE 2. Forrest classification

	Classification	Prevalence (%)	Rebleeding (%)
Active hemorrhage	IA – spurting	10	90
	IB – oozing	10	10 to 20
Signs of recent hemorrhage	IIA – nonbleeding visible vessel	25	50
	IIB – adherent clot	10	25 to 30
	IIC – haematin covered flat spot	10	7 to 10
	III – clean bed of ulcer	35	3 to 5

Study conducted by Pang et al.<sup>(42)</sup> reported higher sensitivity, specificity, and accuracy of GBS in comparison with both clinical and total RS, for the selection of patients for early discharge, but also to identify high-risk group that may present worse outcomes.

Publications from developed countries have shown that only half of the patients returned for outpatient endoscopy after discharge<sup>(47)</sup>. On the current reality of Brazil's public health system, where we imagine that adherence to medical treatment is worse, it seems to be most safety and effective to recommend to all patients admitted with UGB to perform endoscopy before discharge, or at least schedule outpatient endoscopy for the next day in cases of low-risk group (GBS=0).

**Endoscopic classification of Forrest**

In patients with UGB due to ulcers the presence of stigmata of active or recent hemorrhage is correlated with the risk of recurrence of bleeding (Table 2)<sup>(34)</sup>.

Endoscopic findings of active hemorrhage (Forrest IA and IB), nonbleeding visible vessel (Forrest IIA), and adherent clot (Forrest IIB), are grouped as high-risk of rebleeding. The findings of haematin covered flat spot (Forrest IIC) and clean bed of ulcer (Forrest III) are, in turn, grouped as low-risk.

**Initial clinical treatment**

It is recommended that treatment of patients with UGB be performed in an ICU when dealing with elderly, with comorbidities, suspicion of variceal hemorrhage, initial presentation with active bleeding and/or hemodynamic instability<sup>(14, 26)</sup>. (Class I, Level B).

The hemodynamic parameters of pulse oximetry, cardiac monitoring, blood pressure, and urine output, must be obtained regularly in all patients. Fasting should be maintained due to the need of endoscopy in the first hours of admission<sup>(14)</sup>.

Patients with massive bleeding, hematemesis, respiratory failure, or altered level of consciousness, should be evaluated

for orotracheal intubation, for airway protection, and to ensure adequate tissue oxygenation<sup>(14, 19)</sup> (Class I, Level B).

### Fluid resuscitation

The hemodynamic stabilization before endoscopy is a priority, and modifies the natural history of UGB with significant reduction of mortality<sup>(6)</sup>. It is recommended to obtain two peripheral venous access for crystalloids infusion, with goal of achieving a systolic blood pressure of 90 to 100 mmHg, and heart rate below 100 bpm<sup>(11, 14)</sup>. (Class I, Level B).

### Blood transfusion and coagulation disorders

Blood transfusion indication should take into consideration the presence of comorbidities, hemodynamic condition and markers of tissue hypoxia, rather than a fixed level of hemoglobin.

It is recommended red blood cell (RBC) transfusion for maintenance of serum hemoglobin between 7 and 8 g/dL<sup>(7, 20, 26)</sup>. (Class I, level B) Elderly patients or with heart disease may require higher levels of hemoglobin<sup>(11)</sup>.

Platelets transfusion and correction of coagulation disorders, with use of fresh-frozen plasma, vitamin K or protamine sulfate should be considered in patients with severe bleeding and using antiplatelet drugs and/or blood thinners. However, these therapeutic measures should not delay endoscopy<sup>(7)</sup>.

There is no consensus for the correction of coagulopathy and thrombocytopenia of patients with UGB and advanced cirrhosis<sup>(11, 20)</sup>. However, cirrhotic patients with active bleeding and severe thrombocytopenia (50,000</math><math>/\mu\text{L}</math>) or coagulopathy (RNI>1.5) should be evaluated for platelet and/or and/or plasma transfusion<sup>(26)</sup>. (Class IIb, Level B).

### Gastric lavage

Gastric lavage with nasogastric tube in patients with UGB remains controversial. Study with patients admitted because of UGB showed that gastric lavage was associated with shorter time to endoscopy. However, there was no reduction in mortality, costs, blood transfusion or surgery in patients treated with gastric lavage<sup>(30)</sup>.

Another publication reported that nasogastric aspirate without evidence of bleeding presented a negative predictive value of 85% for the diagnosis of high-risk lesions<sup>(2)</sup>. However, currently, there is no study to show that those patients with negative findings do not require endoscopy, or even that they can wait safely for later endoscopic evaluation.

Therefore, there is no consensus for routine use of gastric lavage with nasogastric tube. In our opinion, this procedure may be reserved if gastric chamber cleaning is needed, for removal of blood and clots in order to facilitate endoscopic examination.

### Prokinetic agents

The use of prokinetic agents on UGB aims to empty the stomach before endoscopy, which can improve the evaluation of gastric mucosa, the identification of bleeding lesions, and may reduce the need for a second endoscopy.

Recent meta-analysis comparing erythromycin with placebo demonstrated a significant increase in the incidence of

gastric emptying using erythromycin, with significant reduction of the need for a second endoscopy, amount of blood transfusion, and length of hospital stay<sup>(5)</sup>.

Therefore, we recommend the use of erythromycin IV (intravenous route) at a dose of 250 mg, diluted in 100 mL of physiological saline, with infusion in 30 min and about 30 to 60 minutes before endoscopy, in patients with UGB and suspected of having significant amount of blood and clots inside stomach. (Class I, Level A).

Erythromycin IV is an approved drug in Brazil, and available for use as the erythromycin lactobionate (Tramoxil<sup>®</sup>, Opem Pharmaceuticals, Brazil).

### Proton pump inhibitors

Meta-analysis by Laine et al.<sup>(35)</sup> demonstrated that intravenous infusion of proton pump inhibitors (PPIs), in high doses (bolus of 80 mg, followed by 8 mg/h for 72 h), in patients with UGB by peptic ulcers with high-risk findings, compared with placebo, significantly reduced rebleeding, surgery and mortality. (Class I, Level A). In this same study, lower doses of PPIs also reduced rebleeding, but had no significant influence on need for surgery and mortality.

Another recent meta-analysis reported that there is insufficient data for concluding superiority, inferiority or equivalence of high dose PPIs infusion over lower doses in UGB secondary to peptic ulcers<sup>(41)</sup>. In conclusion, the authors recommended the use of high doses PPIs infusion, based on the existence of a larger amount of evidence with this treatment.

An important issue is the introduction of high doses PPIs treatment before endoscopy in patients with suspected bleeding ulcer. This practice proved to be a cost-effective strategy, in comparison with placebo and the use of high doses PPIs only after endoscopy, with reduction of cases with ulcers and high-risk stigmata and decreasing the need for endoscopic therapy<sup>(3, 7)</sup>. (Class IIa, Level A).

### UGB and *Helicobacter pylori*

*Helicobacter pylori* (HP) is the main etiological factor of peptic ulcers. The HP infection rate in patients with bleeding ulcer is about 80%. Meta-analysis of Gisbert et al.<sup>(27)</sup> demonstrated that the eradication of HP, compared with antisecretory non-eradication therapy, significantly decreased rebleeding.

Therefore, all patients with UGB secondary to peptic ulcer must be tested for HP infection, and if the infection is detected the eradication therapy should be offered. (Class I, Level A).

Among the tests available for HP infection, the rapid urease test performed during endoscopy is the most widely used, because of low cost, easy execution and fast result. However, diagnostic tests for HP infection have low negative predictive value during acute bleeding, with 25% to 55% of false-negative results<sup>(7)</sup>. These findings suggest caution in interpreting of an initial negative test, as well as it is recommended to repeat a negative test during follow-up<sup>(7)</sup>.

Prospective study reported that HP infection did not influence the rebleeding rate in the first three weeks after UGB secondary to ulcer<sup>(46)</sup>. Thus, there is no need to treat

patients with HP infection before the oral route can be safely established.

### Antibiotic prophylaxis

Gastrointestinal bleeding is an independent risk factor for the development of bacterial infection, and the presence of infection in cirrhotic patients with UGB results in higher rates of rebleeding and mortality<sup>(9)</sup>.

Meta-analysis showed that the use of prophylactic antibiotics, for a short period in patients with cirrhosis and UGB, with or without ascites, compared with the absence of prophylactic antibiotic therapy, significantly reduced the incidence of bacterial infections, length of hospital stay, rebleeding and mortality<sup>(16)</sup>. (Class I, Level A).

The prophylactic therapy with norfloxacin 400 mg orally every 12 hours for 7 days is the most widely used and recommended in medical practice, and should be started during hospital admission, even before endoscopy<sup>(11, 26)</sup>. Other similar antibiotic, such as ciprofloxacin (500 mg, every 12 hours), can be used. Quinolones may also be administered intravenously, when the oral route is not possible<sup>(20, 26)</sup>.

Study conducted by Fernández et al.<sup>(22)</sup> compared the use of intravenous ceftriaxone (1 g/day) with norfloxacin oral (400 mg every 12 hours), both therapies for 7 days, in patients with advanced liver cirrhosis and UGB. The infection rate was significantly higher in the group that received oral norfloxacin. (Class IIa, B Level).

### Vasoactive drugs

Vasoactive drugs act decreasing variceal blood flow by mesenteric and splenic veins constriction. The vasoactive drugs most used in Brazil are: somatostatin, octreotide, vasopressin, and terlipressin.

Vasoactive drugs should be started immediately upon suspicion of variceal UGB, even in pre-hospital setting and before endoscopy<sup>(11, 20, 26)</sup>. (Class I, Level A).

Vasopressin was the first vasoactive drug used for treatment of variceal UGB, but studies have shown that its use is associated with serious adverse events<sup>(26)</sup>. Somatostatin and octreotide have a good safety profile, with rare serious adverse effects and can be used continuously for up to 5 days<sup>(26)</sup>.

Terlipressin is a synthetic derivative of vasopressin with long action, which features significantly reduced frequency and severity of side effects when compared to vasopressin. Terlipressin was the only drug that produced mortality reduction in patients with cirrhosis with UGB<sup>(33)</sup>. Thus, terlipressin has been recommended as the vasoactive drug of choice in variceal UGB.

Terlipressin (Glypressin®, Ferring Pharmaceuticals, Brazil) is an approved and available drug in Brazil. It is suggested a loading dose of 2 mg, with maintenance dose every 4 hours according to body weight: 1.0 mg for patients with up to 50 kg; 1.5 mg for weight between 50 and 70 kg; and 2.0 mg for more than 70 kg<sup>(24)</sup>. The therapy should be maintained until the bleeding has been controlled for 12 hours. In addition, duration of drug therapy can be extended for up to 3 to 5 days, if necessary<sup>(20, 24)</sup>.

Table 3 summarizes the vasoactive drugs available in Brazil, with its doses and major adverse effects.

### Endoscopic treatment

Endoscopy is the method of choice for diagnosis and treatment in the UGB, and should be performed as soon as possible after admission.

#### 1. Endoscopy on the management of nonvariceal UGB

Endoscopy should be performed in the first 24 hours in patients with suspected nonvariceal UGB, because it enables early discharge in the low-risk group, and in the high-risk group is associated with reduction of blood transfusion, rebleeding, surgery and length of hospital stay<sup>(18)</sup>. (Class I, Level A).

Study of Lim et al.<sup>(38)</sup> showed that endoscopy performed within 13 hours of presentation, in selected high-risk patients, defined by GBS  $\geq 12$ , was associated with lower mortality.

Endoscopic therapy is indicated for patients with peptic ulcers and high-risk findings, such as active bleeding (Forrest I) or a visible vessel (Forrest IIA)<sup>(7)</sup>. Endoscopic therapy for ulcers with adherent clot (Forrest IIB) is controversial, since there are conflicting results in literature. It is recommended to consider endoscopic hemostatic therapy especially in patients with high-risk of rebleeding, through the RS and/or GBS<sup>(7)</sup>. Patients with peptic ulcers and low-risk stigmata, such as haematin covered flat spot (Forrest IIC) or clean base (Forrest III), do not require endoscopic treatment<sup>(7)</sup>.

Several meta-analyses have shown that, in cases of UGB secondary to ulcers with high-risk stigmata, combination therapy with epinephrine in association to a second endoscopic method, such as cauterization, clips or injection of a second agent, compared to monotherapy with epinephrine injection, showed lower risk of rebleeding, surgery and mortality<sup>(8)</sup>. (Class I, Level A).

We recommended the combination therapy, or monotherapy with cauterization or clips, for endoscopic hemostatic therapy of ulcers with high-risk stigmata.

In patients with nonvariceal UGB due to Mallory-Weiss syndrome, esophagitis, Dieulafoy lesion, or gastric antral vascular ectasia, the endoscopic treatment can be realized with cauterization or clips. Cases of UGB secondary to upper gastrointestinal tract cancers can be treated endoscopically with cauterization or injection method. However, the rebleeding rate is high. Surgical treatment, radiotherapy and hemostatic embolization have better results, with lower rebleeding<sup>(32)</sup>.

#### • Second-look endoscopy

Second-look endoscopy is defined as scheduled second endoscopy performed 16 to 24 hours after initial endoscopic hemostatic therapy. Its goal is repetition of endoscopic treatment in cases with persistent high-risk lesions<sup>(7)</sup>.

Study of Chiu et al.<sup>(17)</sup>, with control group treated with high doses PPIs and endoscopy with combination therapy, did not show improvement in clinical outcomes when the second-look endoscopy was performed systematically.

TABLE 3. Vasoactive drugs used in variceal UGB

Drug	Loading dose	Maintenance dose	Side effects	Note
Vasopressin	0.4 to 1 U/min	0.4 to 1 U/min for 48 h	AMI, arrhythmias, and stroke	Associate nitroglycerin (20 mg/day)
Somatostatin	250 µg (up to 3 times in 1 h)	250 µg/h for up to 5 days	nausea, vomiting, and hyperglycemia	500 µg/h in critical patients
Octreotide	50 µg	25 to 50 µg/h for up to 5 days	nausea, vomiting, and hyperglycemia	
Terlipressin	2 mg	1 to 2 mg every 4 h for up to 3 to 5 days	abdominal pain	

UGB: upper gastrointestinal bleeding; AMI: acute myocardial infarction.

Additionally, the strategy of second-look endoscopy, in selected patients at high-risk of rebleeding, was most effective and with lower costs than the strategy of second-look for all patients<sup>(7)</sup>. (Class IIa, B Level).

## 2. Endoscopy on the management of variceal UGB

Endoscopy on suspicion of variceal UGB should be performed in first 12 hours after admission, since delayed endoscopy is an independent risk factor for in-hospital mortality<sup>(29)</sup>. (Class I, Level A).

### • Endoscopic therapy for esophageal varices

Methods of endoscopic hemostatic therapy for bleeding esophageal varices are endoscopic sclerotherapy (EST) and the endoscopic variceal ligation (EVL).

#### • Endoscopic sclerotherapy

The EST may be done by direct intravariceal injection of the sclerosant, or by paravariceal injection adjacent to variceal veins. Multiple sclerosants agents can be used (sodium tetradecyl sulfate, sodium morrhuate, ethanolamine oleate, polidocanol, ethanol, and cyanoacrylate), with good results and similar efficacies.

The EST is an effective treatment during acute variceal hemorrhage, with immediate control of bleeding in more than 90% of cases, and with significant reduction of rebleeding<sup>(32)</sup>.

#### • Endoscopic variceal ligation

Majority of studies reported superiority of EVL compared to ES, regarding to lower complications, rebleeding and mortality<sup>(32)</sup>. We recommended EVL as the treatment of choice in acute hemorrhage of esophageal varices. However, the ES should remain as an option when the EVL is not available, or when this is not possible due to technical difficulties<sup>(11, 26)</sup>. (Class I, Level A).

#### • Endoscopic therapy for gastric varices

Gastric varices occur in up to 25% of patients with portal hypertension, and mostly associated with esophageal varices. Endoscopic treatment of choice in acute bleeding of fundal varices (GOV2 and IGV1) is the cyanoacrylate injection<sup>(11, 20)</sup>. (Class I, Level B).

The hemostasis rate with cyanoacrylate injection is about 90%, and the comparison with other endoscopic methods, such as EVL, showed better rates of hemostasis, rebleeding and obliteration with cyanoacrylate<sup>(39)</sup>.

### • Secondary prophylaxis of variceal UGB

Patients who have recovered from an episode of variceal UGB should receive secondary prophylaxis with endoscopic eradication of variceal veins, once bleeding recurrence without the treatment is approximately 60% in 1 to 2 years, with 33% mortality<sup>(26)</sup>.

In secondary prevention of esophageal variceal bleeding, combination of endoscopic treatment with nonselective beta-blocker (NSBB) reduced the risk of new bleeding, when compared with endoscopic therapy or NSBB alone (propranolol or nadolol)<sup>(28)</sup>. (Class I, level A).

Propranolol is a widely available NSBB in Brazil. Its recommended its introduction after hemodynamic compensation, usually on the sixth day after bleeding episode. The initial dose is 20 mg, orally, every 12 hours, and should be adjusted to the maximum dose tolerated by patient<sup>(11, 20, 26)</sup>.

Regarding to the endoscopic therapy of choice in secondary prophylaxis of esophageal varices, studies reported superiority of EVL compared to EST, because the eradication was obtained with less complications, shorter time and fewer number of sessions with EVL<sup>(26)</sup>. Endoscopic therapy with EVL must be performed every 1 to 3 weeks until the esophageal varices are eradicated, which typically occurs after 2 to 4 sessions<sup>(11, 26)</sup>.

In the secondary prophylaxis of bleeding fundal varices, the cyanoacrylate injection significantly reduced rebleeding and mortality, when compared with propranolol<sup>(40)</sup>.

### Persistent bleeding and rebleeding

Although majority of cases with UGB is controlled with endoscopic therapy, until 20% of cases failed to treatment or present rebleeding<sup>(7, 26)</sup>. Persistent bleeding and rebleeding definitions vary in literature. However, the concept of persistent bleeding, or failure to endoscopic treatment, refers to bleeding which is not controlled after endoscopy. Rebleeding is defined as a new bleeding episode after successful endoscopic therapy, within the first 30 days after the hemorrhage<sup>(36)</sup>.



Cases of persistent bleeding or rebleeding usually present with the following findings<sup>(20, 36)</sup>: new hematemesis or bloody nasogastric aspirate; new episode of melena; signs of hemodynamic instability (tachycardia, hypotension); and/or hemoglobin drop  $\geq 2$  g/dL, or need of RBC transfusion  $\geq 2$  units, in 24 hours.

A second endoscopic attempt to control hemorrhage can be performed in cases of persistent bleeding or rebleeding<sup>(7, 11)</sup>. (Class IIa, B level). A different endoscopic method from the previously used should be considered for retreatment.

Patients with persistent bleeding or rebleeding, when the hemorrhage is not stopped quickly and effectively with a second endoscopic attempt, should be referred for rescue therapies.

### Rescue therapies on nonvariceal bleeding

#### • Surgery

Surgical treatment in nonvariceal UGB is reserved, traditionally, to cases with bleeding ulcer refractory to endoscopic treatment<sup>(7)</sup>. (Class IIa, B Level). Surgery has high success rate in controlling the bleeding, however may present mortality of up to 36%<sup>(1)</sup>.

#### • Transarterial embolization

Transarterial embolization (TAE) has been studied as a therapeutic alternative to surgery in cases of nonvariceal UGB with failure to endoscopic therapy, especially in the patients with high surgical and anesthetic risk<sup>(7)</sup>. (Class IIa, B Level) Studies have shown a technical success rate around 85% with TAE. And in comparison with surgery there was fewer complications, but with higher rate of rebleeding<sup>(50)</sup>.

### Rescue therapies on variceal bleeding

#### • Balloon tamponade

Balloon tamponade (Sengstaken-Blakemore tube) has high effectiveness in the immediate control of variceal bleeding, successfully in about 80% of cases. However, should only be used temporarily (maximum 24 hours) in cases of variceal UGB with uncontrolled hemorrhage after endoscopy, due to high rates of rebleeding and potentially lethal complications<sup>(20, 26)</sup>. (Class IIa, B Level). Orotracheal intubation for airway protection is strongly recommended before use of balloon tamponade.

#### • TIPS

TIPS (transjugular intrahepatic portosystemic shunt) is currently recommended as rescue therapy of choice in variceal bleeding refractory to endoscopy, with high technical and clinical success rate<sup>(11, 26)</sup>. (Class I, Level A).

Recently, clinical trial demonstrated that in patients with cirrhosis (Child B or C until 13 points) and variceal bleeding, who received vasoactive drugs and endoscopic therapy, early TIPS within 72 hours after endoscopy has reduced rebleeding and mortality<sup>(25)</sup>. This procedure was considered by Baveno V consensus<sup>(20)</sup>, and will also be recommended by the next

Baveno VI, as it was presented during the Digestive Disease Week 2015. However, we believe that further studies should be conducted, in different populations, for external validation of those findings and subsequent introduction of this procedure in our clinical practice.

#### • Surgery

Shunt surgery is reserved only for patients with variceal bleeding refractory to clinical and endoscopic therapy. It has high hemostasis rate, but with significant postoperative risk of hepatic encephalopathy, and ideally should be performed in Child A patients<sup>(11, 26)</sup>. (Class IIa, level B).

#### • Self-expanding metal stent

Recent studies of case series have demonstrated good results with self-expanding metal stents (SEMS) for cases of bleeding esophageal varices after failure to endoscopic therapy<sup>(21)</sup>. However, further evaluation is still needed with randomized studies<sup>(20)</sup>.

#### Hemostatic powder

Recently, some reports showed good outcomes in controlling variceal and nonvariceal UGB with the use of hemostatic powder (Hemospray<sup>®</sup>, Cook Medical, Winston-Salem, North Carolina, USA) in some European countries<sup>(49)</sup>. The results are promising, especially because it is an easy technique to perform even in cases of active or severe bleeding; however, there are only few studies and little experience with this new tool.

#### Schistosomiasis and variceal UGB

The *Schistosoma mansoni* infection is the main cause of noncirrhotic portal hypertension in Brazil, and bleeding from variceal veins is a significant complication of this pathology. There are currently insufficient data on clinical and endoscopic therapy of variceal bleeding in patients schistosomiasis. However, due to the theoretical benefits, we suggest the same recommended practices for patients with liver cirrhosis<sup>(11)</sup>.

### RESULTS: clinical care pathway for UGB

#### Inclusion criteria

Inclusion criteria are the presence of recent upper GI bleeding (in the first 24 hours), described as hematemesis or melena, in patients admitted at the emergency room or ICU.

#### Exclusion criteria

Exclusion criteria were age <18 years, and pregnancy.

#### Additional cases

Cases with hemoglobin drop  $\geq 2$  g/dL in 24 hours, or need of RBC transfusion  $\geq 2$  units, where the main hypothesis is UGB, may also be included.

#### Clinical care pathway for UGB

The clinical care pathway for management of patients with UGB is presented in Figure 3.

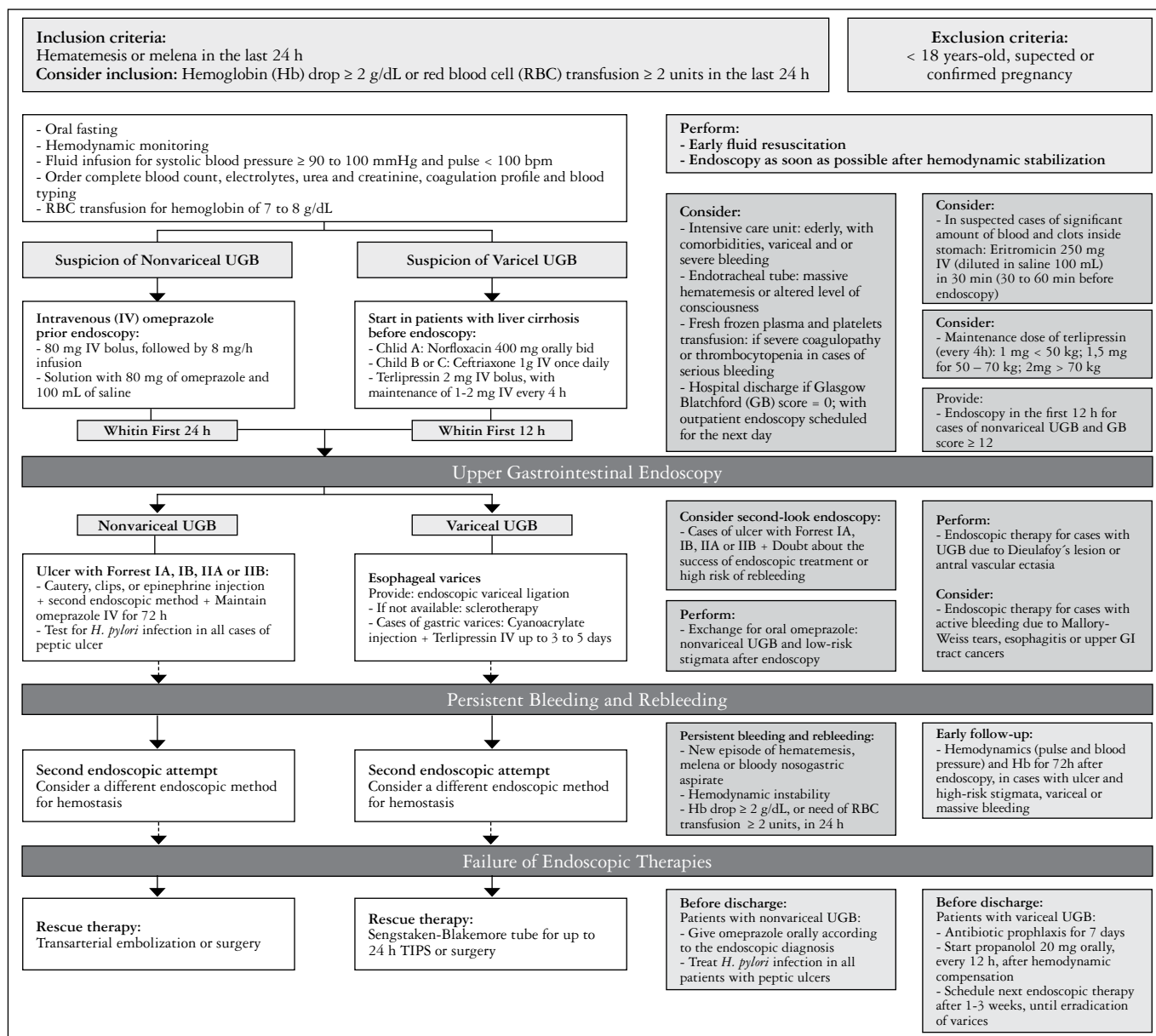


FIGURE 3. Clinical pathway for upper gastrointestinal bleeding (UGB)

### Follow-up after endoscopic therapy

We recommended hemodynamic monitoring (pulse and blood pressure), and serum hemoglobin level, in the first 72 hours after endoscopy, of cases with ulcers and stigmata of high-risk, and in cases of variceal bleeding or other etiology with severe hemorrhage.

### DISCUSSION

Considering the high incidence of UGB in our tertiary hospitals, with important repercussions on mortality and elevated financial costs to the health system, as well as the

need for emergency supportive care by a multidisciplinary team, it is desirable the existence of a clinical pathway for the management of patients with upper GI bleeding.

Between 2008 and 2010, the Brazilian Society of Digestive Endoscopy, the Brazilian Society of Hepatology, and the Brazilian Federation of Gastroenterology, published guidance on nonvariceal UGB<sup>(48)</sup>, guideline on portal hypertension with variceal bleeding<sup>(19)</sup>, consensus on variceal bleeding<sup>(11)</sup>, and guideline on digestive bleeding<sup>(23)</sup>. In all studies, the authors performed an extensive literature review, graded the evidences and issued the recommendations. The guidelines were developed in association with the Brazilian



Medical Association (AMB). All the texts are available online for download at the societies and AMB websites. We felt that the development of a clinical care pathway for the management of patients with UGB could be a possible way to help to implement the actions of the above mentioned Societies.

We updated the extensive literature review on UGB and found several class I and II recommendations on the evaluation and treatment of UGB. We also assessed the structure and resources of a tertiary Brazilian hospital in order to reassure that the recommendations could be locally implemented. The final product of the present research was a compact and comprehensive algorithm for the management of patients with UGB.

In conclusion, the use of this algorithm can enable standardization of medical practices, diffusion of current therapies, decreasing the waiting time for medications and

services, possibly decreasing in length of stay and hospital costs, improvement in the teaching and training of medical students and junior doctors, and especially can promote a better service to patients.

#### Authors' contributions

Franco MC: conception and design; analysis and interpretation of the data; drafting of the article. Nakao FS: conception and design; analysis and interpretation of the data. Rodrigues R: critical revision of the article for important intellectual content. Maluf-Filho F: critical revision of the article for important intellectual content. Paulo GA: critical revision of the article for important intellectual content. Libera ED: conception and design; critical revision of the article for important intellectual content; final approval of the article.

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Franco MC, Nakao FS, Rodrigues R, Maluf-Filho F, Paulo GA, Libera ED. Proposta de modelo de atendimento da hemorragia digestiva alta. *Arq Gastroenterol.* 2015,52(4):xxx.

**RESUMO - Contexto** - A hemorragia digestiva alta implica em significativas repercussões clínicas e econômicas. O estabelecimento correto das mais recentes terapêuticas para a hemorragia digestiva alta está associado à redução na mortalidade intra-hospitalar. O uso de algoritmos para atendimento da hemorragia digestiva alta está associado com menor tempo de internação e menores custos hospitalares. **Objetivos** - O objetivo primário é a criação de um protocolo de atendimento da hemorragia digestiva alta, para ser utilizado em hospital terciário. **Métodos** - Realizada extensa revisão da literatura sobre as condutas na hemorragia digestiva alta, contidas nas bases de dados primária e secundária. **Resultados** - O resultado é um modelo de atendimento para os pacientes com hemorragia digestiva alta e com evidência de sangramento recente, dado por melena ou hematêmese nas últimas 24h, que são atendidos nas salas de emergência e unidades de terapia intensiva de hospitais terciários. Neste protocolo de atendimento, desenhado de forma compacta e compreensível, fica bem evidenciado o manejo dos pacientes desde a admissão, com definição dos critérios de inclusão e exclusão, passando considerações acerca do atendimento clínico inicial, posterior direcionamento para a terapêutica endoscópica, e encaminhamento às terapias de resgate em casos de sangramento persistente ou recorrente. Destacam-se também os cuidados que devem ser tomados antes da alta hospitalar para todos os pacientes que se recuperam de um episódio de sangramento. **Conclusão** - A introdução de um protocolo para atendimento e tratamento de pacientes com hemorragia digestiva alta pode contribuir para uniformização de condutas médicas, diminuição no tempo de espera por medicações e serviços, no tempo de internação e nos custos hospitalares.

**DESCRITORES** - Hemorragia gastrointestinal. Hematemese. Melena. Endoscopia. Procedimentos clínicos. Protocolos clínicos.

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