Upper gastrointestinal tract bleeding management : Belgian guidelines for adults and children

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Abstract

Upper gastrointestinal bleeding (UGIB) remains a common disease affecting 100 to 170 per 100 000 adults per year and causing thereby a significant burden to healthcare resources. Despite the improvements in the management of this disorder, the associated mortality ranges from 5 to 14%.

Since the general management of UGIB is not uniform, the main objective of this work is to provide guidelines for the care of adults and children presenting with bleeding caused by gastro-duodenal ulcer or variceal rupture.

Methods : In the absence of evidence-based recommendations, these guidelines were proposed after expert opinions reconciliation and graded accordingly. They are based on the published literature up to September 2010 and graded according to the class of evidence.

Results : The current guidelines for the management of UGIB include recommendations for the diagnostic process, general supportive care, pharmacological therapy aiming at bleeding control, specific and endoscopic treatment of acute bleeding and follow-up for both gastro-duodenal ulcers and portal hypertension-induced bleeding. (Acta gastroenterol. belg., **2011**, 74, **45-66**).

Key words : upper gastrointestinal bleeding, varices, ulcers, treatment, guidelines, endoscopy.

Introduction

Introduction

Upper gastrointestinal bleeding (UGIB) is a common disorder with an important burden on healthcare resources. Its incidence in Europe is around 1-2/1000 inhabitants and UGIB is still associated with a mortality rate of 5-14%. Gastro-duodenal ulcers and other erosive lesions account for most of the cases (80%). Portal hypertension represents about 10 to 15% of UGIB episodes with 75% related to oesophageal variceal bleeding and 20% to gastric variceal bleeding (1). Upper gastrointestinal endoscopy is the standard of care in the diagnosis and in the first-line treatment of UGIB. It reduces recurrent bleeding, need for surgery and mortality (2). However, management of UGIB involves many other aspects of care including resuscitation, transfusion, medical therapy, radiological interventions or surgery.

There is considerable variability in the management of these different aspects of the care of UGIB between different European countries and between hospitals within the same country (3,4). In addition, various specialists including general practitioners, emergency physicians, gastroenterologists and hepatologists, intensivists, radiologists and surgeons may be involved in the management of UGIB augmenting the potential for variability and a less than optimal care. We therefore considered that interdisciplinary guidelines for the management of UGIB based on current standards for Evidence Based Medicine (EBM) would provide an opportunity for clinicians to improve the management of their patients with UGIB. We do not believe that guidelines are mandatory tenets appropriate for all patients. Clinical guidelines should constitute a canon or principle tailored to the individual patient (5). In addition, EBM might provide quality indicators for the assessment of care to bleeding patients at a local, national or international level as recently published (6).

Processes and methods to define the Belgian guidelines

The current guidelines have been based on the published literature up to September 2010 and graded according to the class of evidence (Table 1). Where EBM recommendations were lacking, guidelines were proposed on reconciled expert opinions and commented in the manuscript.

Table 1. — **Level of evidence and grade of recommendations**

Level of Evidence	Grading Criteria	Grade of Recommendation
1a	Systematic review of RCT's including meta-analysis	A
1b	Individual RCT with narrow confidence interval	A
1c	All or none RCT's	B
2a	Systematic review of cohort studies	B
2b	Individual cohort study and low quality RCT	B
2c	Outcome research study	C
3a	Systematic review of case-control studies	C
3b	Individual case-control studies	C
4	Case series, poor quality cohort and case control studies	C
5	Expert opinion	D

RCT : randomized controlled clinical trial.

General management of UGIB before endoscopy

Establishing a tentative diagnosis

Endoscopy is the gold standard for diagnosing the cause of UGIB. Until the time of endoscopic investigation, the history of the patient (if necessary and if available through next of kin) and the clinical presentation will help to establish a tentative diagnosis. A tentative diagnosis of variceal bleeding will lead to a different management strategy than for non-variceal bleeding (5-D). Any physician having the initial contact with a patient presenting with signs of UGIB should certainly attempt to answer at least the following four questions at the very beginning of the approach to the patient :

1) Does the patient have a history of aortic aneurysm with or without surgery ? If the answer is yes and the patient is hemodynamically stable, the initial investigation should not be endoscopy but contrast CT scan. If the patient is unstable, prompt surgical expert advice must be sought for with the option of immediate surgery because bleeding from an aorto-enteric fistula is highly probable (5-D).
2) Is the history or clinical examination suggestive of bleeding related to portal hypertension ? If the answer is yes, vasoactive medication must be started immediately (1-A).
3) Does the clinical examination suggest impaired vital organ function (tachycardia, hypotension, tachypnea, altered consciousness, cold extremities) ? If the answer is yes, the patient should be placed in a monitored environment immediately, contact should be established with an emergency physician or intensive care specialist and the initial lab investigation should include lactate measurement and blood typing and cross-matching (5-D).
4) Is the patient taking anticoagulant or antiplatelet therapy ? *Vide infra.*

Resuscitation

Any patient with tachycardia above 100/min or a systolic blood pressure < 100 mmHg or an increased lactate should be considered for volume replacement. Analogous to patients presenting with severe sepsis or septic shock, the target for volume loading is a mean arterial blood pressure (MAP) > 65 mmHg and/or a systolic blood pressure > 100 mmHg (5-D) (7). In patients with a tentative diagnosis of non-variceal bleeding 2 litres of crystalloids followed by colloids constitute a reasonable initial approach. In patients with a strong suspicion of variceal bleeding due to liver cirrhosis, albumin 5% is deemed to be the preferred volume expander (5-D). Once hemodynamic targets have been reached and in the absence of contra-indications due to cardiac or renal co-morbidity, volume replacement at 30 mL/kg per 24 h is appropriate.

In patients with persistent hypotension (MAP < 65 mmHg) for more than 30 minutes in spite of vigorous fluid loading, temporary normalization of MAP with a vasopressor can minimize or prevent subsequent organ dysfunction. The vasopressor of choice in this setting is noradrenalin (5-D). In case of variceal bleeding, terlipressin can be a valid alternative (5-D).

Blood transfusion

Based on a large randomised trial in critically ill patients, transfusion of packed red blood cells above 8 g/dL confers no benefit for outcome. In patients with a history of coronary or cerebrovascular diseases the transfusion trigger is higher and set at 9-10 g/dL (1-B).

Intubation and sedation

It is well known that endoscopy performed in optimal conditions is associated with a better control of bleeding, shorter intensive care unit (ICU) and hospital stay (1b-A). Unfortunately, there is a complete absence of

randomized trials and a paucity of trials in general that have been looking at whether or not prophylactic intubation might improve outcome in patients with UGIB (8-10). The existing literature is exclusively based on retrospective studies and the data suggest that prophylactic intubation in both variceal and non-variceal bleeding does not change the incidence of cardiovascular events, aspiration pneumonia or mortality (4-C) (8-11). However, common sense supports that endotracheal intubation should be performed before endoscopy in patients with ongoing hematemesis, hemodynamic instability in spite of volume loading, agitation with the absence of co-operation or Glasgow Coma Scale (GCS) < 8 (5-D) (12). An additional indication for intubation is the patient that becomes agitated or suffers from renewed hematemesis during the endoscopic procedure (5-D).

What is a high-risk patient ? Who should be transferred to an ICU ?

Currently, 2 scores are widely used for assessing patient's risk of adverse outcome (need for transfusion, rebleeding or death). The Rockall score is the oldest published and integrates endoscopic variables to predict the risk of mortality or of recurrent bleeding (Table 2) (13,14).

However, until endoscopy several decisions will have to be made which depend very much on whether or not the patient has a high risk profile. A modified admission Rockall score was developed without including endoscopic variables, but it is less powerful as predictor. More recently, the Glasgow Blatchford bleeding score (GBS) was described which includes simple admission variables (15) (Table 3). The GBS has been validated in different countries and is more powerful than both the admission and full Rockall scores in predicting the need for transfusions, endoscopic treatment, surgery or death (16). Moreover, it allows to safely select patients with very low risk (GBS = 0), to be managed as outpatients (17). A patient should be classified as high risk in the presence of a GBS ≥ 8 (2-B). These patients should be transferred to an ICU as soon as possible. Other patients that may clearly benefit from ICU care are those with persistent bleeding in spite of endoscopic therapy and those who have witnessed massive aspiration of blood (5-D).

Vasoactive medication before endoscopy

Vasoactive medication for suspected variceal bleeding (oesophageal and gastric varices)

The aim of using vasoactive drugs is to cause splanchnic vasoconstriction, thereby decreasing portal pressure and thus stopping or reducing bleeding from varices. Vasoactive medications in the setting of variceal bleeding are clearly indicated as they stop the bleeding in 75-80% of patients and because they reduce the risk for recurrent bleeding (1a-A). Vasoactive drugs should be started as soon as possible before diagnostic endoscopy, when variceal hemorrhage is suspected. This can be done during transfer to or at arrival at the hospital (1b-A) (18-20). Although optimal duration of the vasoactive drug treatment is not well established, most centres maintain the treatment for 5 days, because this is the period during which the risk of rebleeding is the highest. The recent Baveno V guidelines of May 2010 state that the vasoactive therapy should be continued for 5 days (5-D) (20) ; while the Baveno IV guidelines stated 2 to 5 days (1a-A) (18,20,21).

The choice of vasoactive drug should be based on local availability and efficacy. In the US, only octreotide is available, however evidence for using octreotide in variceal bleeding is very low because of tachyphylaxis (12). In Belgium and Europe octreotide, somatostatin, vapreotide, vasopressin and terlipressin are available. Vasopressin has too many side effects and is not used anymore in variceal bleeding. Terlipressin is a potent splanchnic vasoconstrictor with fewer side effects than vasopressin. Somatostatin has also few side effects and can also be used adjunctively to endoscopic therapy.

Either terlipressin or somatostatin should be used in combination with endoscopic treatment, because combination therapy increases the control of bleeding by another 12% and lowers the risk for rebleeding by

Table 2. — **Rockall score (13,14)**

Variable	Score 0	Score 1	Score 2	Score 3
Age (years)	< 60	60-79	> 80	
Shock	No shock	Heart rate > 100/min	Systolic blood pressure < 100 mmHg	
Comorbidity	No major		Chronic heart failure, ischemic heart disease, major comorbidity	Renal failure, liver failure, metastatic cancer
Diagnosis	Mallory Weiss	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, spurting vessel	

The Rockall risk scoring system identifies patients at risk of adverse outcome following acute UGIB. The total score is calculated by simple addition of the scores for the different variables. A score < 3 carries a good prognosis ; a total score > 8 carries a high mortality risk.

Table 3. — **The Glasgow-Blatchford bleeding score (GBS)** (15)

BLOOD UREA (mg/dL)	SCORE VALUE
39-48	2
49-60	3
61-150	4
> 150	6
HEMOGLOBIN FOR MEN (g/dL)	
12-12,9	1
10-11,9	3
< 10	6
HEMOGLOBIN FOR WOMEN (g/dL)	
10-11,9	1
< 10	6
SYSTOLIC BLOOD PRESSURE (mmHg)	
100-109	1
90-99	2
< 90	3
OTHER MARKERS	
Pulse ≥ 100/min	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2
TOTAL score	

Low risk if Score is "0"
High risk is any score > 0 needing medical intervention, transfusion, endoscopy or surgery
ICU admission is indicated if GBS ≥ 8

Score is "0"only if all the following are present :
1. Hemoglobin level > 12.9 g/dL (men) or > 11.9 g/dL (women)
2. Systolic blood pressure > 109 mm Hg
3. Pulse < 100/minute
4. Blood urea nitrogen level < 39 mg/dL
5. No melena or syncope
6. No past or present liver disease or heart failure.

another 12% (20,22,23). There are no RCT's comparing both drugs combined with endoscopic therapy. However, terlipressin versus placebo has shown improved survival in one small RCT and in a meta-analysis (21,24-26).

Terlipressin improves the rate of bleeding control (within 48 h : 75-80% ; within 5 days 67%) and survival. The dose of terlipressin is an initial intravenous (IV) bolus : < 50 kg = 1 mg ; 50-70 kg = 1.5 mg ; > 70 kg = 2 mg followed by an IV bolus of 1-2 mg every 4 h for 48 h, followed by 1 mg every 4 h till day 5. Contraindications for the use of terlipressin include coronary insufficiency, peripheral vascular disease, pregnancy, heart rhythm disease, severe bronchial asthma, uncontrolled arterial hypertension and epilepsy. The risk for side effects appears to be less when given in continuous IV infusion (e.g. 4-6 mg/24 h) at least for hepatorenal syndrome (27).

Somatostatin treatment starts with a continuous IV infusion of 6 mg/24 h (= 250 μg/h) immediately followed by a bolus of 250 μg IV within 5 minutes. The

bolus can be repeated up to 3 times within 1 hour. In patients with active bleeding at the time of endoscopy, the infusion regimen can be increased up to 12 mg/24 h (= 500 μg/h). Side effects are rare and there are no major contraindications (21,25,28).

When comparing somatostatin with terlipressin, they have the same bleeding control, risk for rebleeding and mortality rate are found to be similar (21).

Vasoactive medications for non-variceal bleeding

In 1997 a meta-analysis of 14 trials that included 1829 patients treated with somatostatin or octreotide compared with histamine-2-receptor antagonists or placebo, concluded that somatostatin may reduce the risk for continued bleeding from acutely bleeding ulcer disease. The authors suggested that large clinical trials were needed in patients carefully stratified by source, severity and type of bleeding were needed. In 2000, a prospective study with 48 patients showed that somatostatin was no more effective than ranitidine. No further evidence has been published in peer-reviewed Journals since then supporting the routine use of somatostatin in peptic upper GI bleeding. Furthermore no study with the current gold standard of acid suppression (i.e. proton pump inhibitors - PPIs) has been conducted in this setting (29,30).

Therefore, there is insufficient evidence to recommend somatostatin or any other vasoactive medication in the routine treatment of suspected non-variceal UGIB (2b-C).

PPI before endoscopy

PPI in non-variceal bleeding

In patients with overt signs of UGIB but without persistent hypovolemic shock, an IV bolus of 80 mg omeprazole, followed by 8 mg/hour for 72 hours, administered after hemodynamic stabilization and before endoscopy, was reported to be effective in accelerating the resolution of signs of bleeding from ulcers and in reducing the need for therapeutic endoscopy. A recent Cochrane meta-analysis confirmed these findings (31) (1a-A). Another 2010 meta-analysis showed that there is no evidence that continuous high dose PPI (8 mg/h for 72 h) has a better outcome than fractionated low dose (2 × 40 mg/d) PPI for active ulcer bleeding (32). Therefore the panel recommends using 2 × 40 mg/d, the first dose being given before endoscopy as soon as a tentative diagnosis of non-PHT related bleeding is made (5-D). In low risk patients tolerating oral medication, the strategy of giving oral PPI before and after endoscopy, with endoscopic hemostasis for those with no major stigmata of recent hemorrhage, is likely to be the most cost-effective (31-38).

PPI in variceal bleeding

There is no evidence for the use of PPI in the setting of active variceal bleeding or after endoscopic therapy (Baveno V) (20).

Antifibrinolytic medication

Seven double-blind randomized trials on tranexamic acid *vs.* placebo have been published to date, most dating from the seventies and eighties. Only one of these trials includes endoscopic treatments and proton pump inhibitors, i.e. the present standard of care. The trial did not find any significant effect of tranexamic acid on clinical outcome measures. There is no indication for the use of antifibrinolytics in the treatment of variceal or non-variceal UGIB (1a-A) (39).

Antimicrobial prophylaxis

In the setting of UGIB, only patients with known or suspected cirrhosis should receive antimicrobial prophylaxis. The initial work-up of these patients should include an active search for infection (blood, ascites and urine cultures) (1a-A). Proposed first line antibiotics are amoxicillin-clavulanic acid, third generation cephalosporins or quinolones according to local resistance patterns. In patients receiving maintenance therapy with quinolones as prophylaxis for spontaneous bacterial peritonitis, third generation cephalosporins are the first choice. Prophylactic antibiotherapy should not be continued for more than 7 days (18,20).

Coagulation disorders, should anti-Vit K medication and/or anti-platelet medication be discontinued in bleeding ?

Antiplatelet drugs and anticoagulants are commonly used for the treatment and the prophylaxis in vascular diseases. Endoscopic therapy in patients with an acute bleeding while using antiplatelet agents (acetyl salicylic acid, clopidogrel, ticlopidine, dual antiplatelet therapy, glycoprotein IIb/IIIa inhibitors…) is both warranted and safe (40,41). Stopping these agents prior to endoscopy may pose unnecessary atherothrombotic risks and therefore needs careful evaluation. On the other side, in patients with clinically significant UGIB, continued administration of antiplatelet drugs or anticoagulants is known to be associated with a high risk of persistent bleeding.

There is no clear recommendation about either how long these drugs should be discontinued, or whether the reversal of anticoagulation should be partial or complete. The individual decision must be based on the balance between the risk of thromboembolism and that of continuing bleeding. The same balance should be considered to determine the timing of reinstitution of these treatments (40-44).

The American Society of Gastroenterology (ASGE) proposed a classification of high or low risk for thromboembolic event, thereby providing a tool to appreciate this balance (Table 4) (40,41).

In non-cirrhotic patients there is good evidence that anti-Vitamin K therapy (AVK therapy), targeted at an INR of 2.5 (range 2-3) is associated with a lower risk of bleeding than therapy targeted at an INR > 3. In patients with UGIB correction of the INR < 2.5 is advised (4-C). Correction to an INR of 1.5 to 2.5 allows successful endoscopic diagnosis and therapy (45).

For patients with serious bleeding and elevated INR (regardless of the magnitude of the elevation), the American College of Chest Physicians recommends to hold the AVK and to give 10 mg vitamin K by slow IV infusion. A supplement of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) is also proposed depending on the urgency of the situation but certainly in a life threatening bleeding (2C) (41).

The timing for resumption of anticoagulation should be individualized taking into account the risk for thromboembolic event (see Table 4). In patients with high risk for thromboembolic event and for rebleeding, the use of unfractionated heparin (UFH) could be considered due to the advantage of a short half-life.

For non-cirrhotic patients using antiplatelets drugs, there are no clear recommendations. Some suggest withholding these medications until hemostasis is achieved, however, due to the long half life of clopidrogel (7 days), stopping the drug will not have any impact on the short term, so endoscopy and treatment are safe under antiplatelet therapy (5-D). In the absence of randomized controlled trials (RCT's) the panel suggests that platelets transfusion could be considered if the platelet count is

Table 4. — **Condition risk for thromboembolic events** (ASGE standards of practice committee for the management of antithrombotic agents for endoscopic procedures) (40)

Higher-risk condition	Low-risk condition
Atrial fibrillation associated with valvular heart disease, prosthetic valves, active congestive heart failure, left ventricular ejection fraction < 35%, a history of a thromboembolic event, hypertension, diabetes mellitus, or age > 75 y	Uncomplicated or paroxysmal nonvalvular atrial fibrillation
Mechanical valve in the mitral position	Bioprosthetic valve
Mechanical valve in any position and previous thromboembolic event	Mechanical valve in the aortic position
Recently (< 1 y) placed coronary stent	Deep vein thrombosis
Acute coronary syndrome	
Non-stented percutaneous coronary intervention after myocardial infarction	

lower than 30,000/μL in case of ongoing bleeding (5-D) (40,44). The timing for resumption of antiplatelet medication should be individualized taking into account the risk for thromboembolic event (Table 4).

In <u>cirrhotic patients</u>, PT/INR is not a reliable indicator of the coagulation status (Baveno V). On the basis of currently available data, in these patients no definite recommendations can be made regarding management of coagulopathy and thrombocytopenia (5-D) (18,20). There is certainly no evidence for administration of coagulation factors prior to endoscopy (5-D). Over-transfusion with fresh frozen plasma (FFP) and platelets cause an increase in portal pressure and may be associated with sustained bleeding (2b-B). In the absence of RCT's the panel suggests that platelets transfusion could be considered if the platelet count is lower than 30,000/μL in case of ongoing bleeding (5-D).

In the patient suffering from an acute coronary syndrome or recently having had placed a vascular stent, no strong recommendations concerning antiplatelet drugs can be made. A cardiologist should always be consulted before stopping any antiplatelet agent, but drugs must be continued in many cases (5-D).

Stomach cleansing before endoscopy

In the case of UGIB, a clean stomach or duodenum during endoscopy is highly desirable. Naso-gastric lavage is associated with complications and fails to be efficient in half of the cases. A recent pharmacologic method for cleansing the stomach has gained a 1a-A evidence for its use before endoscopy after demonstration of effectiveness (46-48) and cost / effectiveness (49) : the IV administration of 250 mg erythromycin over 5 min, 20 min before endoscopy, dramatically increases the rate of empty stomach, decreases the time of endoscopy and the need for a second look. In this setting erythromycin acts as a motilin agonist which induces potent gastric contractions and evacuation of gastric blood clots.

In case of failure to clean the stomach, large operative channel endoscopes or other tricks may be used like an attachable distal cap that can facilitate the removal of blood clots during endoscopic treatment (50).

Feeding and nasogastric tube

Although there are no studies, there are probably no contra-indications to place a nasogastric tube after band ligation or treatment of non-PHT related bleeding unless other recommendation of the endoscopist. Oral feeding can start when the patient is hemodynamically stable and conscious (5-D).

When is tamponade indicated ?

Balloon tamponade is indicated for uncontrolled bleeding from oesophageal/gastric varices for which a definitive therapy is planned within 24 h (1-B) (51). Balloon tamponade is effective in bleeding control

(80%) but rebleeding after balloon deflation is high (50%). The complication rate (aspiration, migration, necrosis and perforation of oesophagus) is high and associated with high mortality. The gastric balloon should be deflated within 24 h to avoid necrosis of the stomach (in case of simultaneous inflation of an oesophageal balloon this one should be deflated every 4 hours).

Linton tamponade (600 mL) can be used for oesophageal and gastric varices (52). Sengstaken Blakemore tamponade can only be used for oesophageal varices (5-D).

Recently a RCT showed that a covered oesophageal stent can be placed for oesophageal varices, however this is not recommended yet and should be confirmed in other studies (12,20,21,53).

Endoscopic and other specific treatment modalities for acute UGIB

Optimal timing for endoscopy ?

The optimal timing for endoscopy for non-PHT related bleeding is within the 24 h of patient's presentation (1a ;A) (54). This allows for safe and prompt discharge of patients classified as low risk, it improves patient outcomes for high risk patients and reduces the use of resources for patients at low or high risk. No evidence exists for any clinical benefit of performing endoscopy within 12 hours of presentation (reduction of rebleeding rate or survival improvement) as this may lead to increased use of endoscopic therapy, which may not be necessary. This correlates to studies showing that performing emergency endoscopy in bad conditions (without adequate human and material resources) is associated with increased recurrent bleeding, need for surgery and hospital stay (2b-B) (55). Besides this statistical evidence, each case should indeed be individually discussed, according to patient's clinical situation and maybe the GBS, as suggested before.
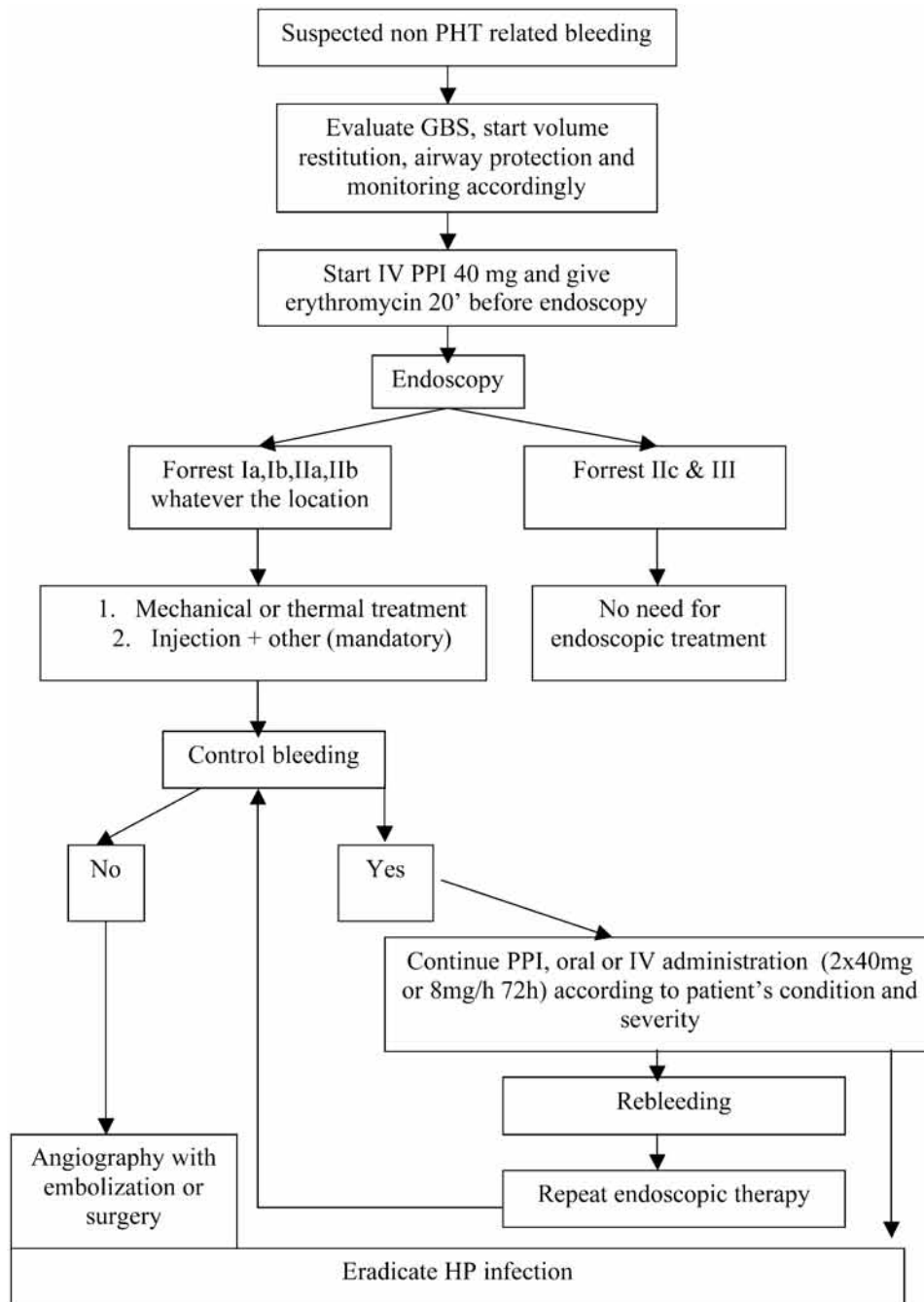
If a variceal bleeding is suspected, endoscopy should be performed as soon as possible but within 12 hours (5-D) (18-20).

Hemodynamically unstable and high risk patients should be transferred to ICU for conditioning and performing endoscopy, after intubation, in proper and safe conditions.

Endoscopic treatment for non-variceal bleeding (Fig. 1)

Ulcers

Endoscopic treatment should be performed at the time of diagnosis by an experienced endoscopist. Lesions that are actively bleeding (Forrest Ia, b) and non-bleeding visible vessels (Forrest IIa) should be treated endoscopically. Clots (Forrest IIb) should be removed by washing, using a basket, snare or a cap (50) until the ulcer base is visible for adequate treatment of the underlying vessel (56,57,58) as the risk of rebleeding after endoscopic treatment from a Forrest IIb ulcer is the same as for a

Suspected non PHT related bleeding

Evaluate GBS, start volume restitution, airway protection and monitoring accordingly

Start IV PPI 40 mg and give erythromycin 20' before endoscopy

Endoscopy

Forrest Ia,Ib,IIa,IIb whatever the location

Forrest IIc & III

1. Mechanical or thermal treatment
2. Injection + other (mandatory)

No need for endoscopic treatment

Control bleeding

No

Yes

Continue PPI, oral or IV administration (2x40mg or 8mg/h 72h) according to patient's condition and severity

Rebleeding

Angiography with embolization or surgery

Repeat endoscopic therapy

Eradicate HP infection

Abbreviations : GBS : Glasgow-Blatchford bleeding score.

Fig. 1. — Algorithm for non-variceal bleeding

Forrest IIa. Ulcers with a clean or black base do not need endoscopic treatment (1a-A). The Forrest classification is described in Table 5.

Hemostasis can be performed using different independent or combined methods.

a. **Injection therapy with saline** is widely applicable, easy, inexpensive and can be used when front view of the bleeding point cannot be maintained. Addition of epinephrine (1:10,000 dilution) or a sclerosant offers no advantage (59). Injection therapy should only be considered as a temporary measure because its effect is only transient. It might allow clearing the endoscopic field (60,56,61,62) (1a-A). This method is not to be considered as a definite treatment but as an adjunct to more efficient and long-lasting hemostatic procedures.

b. **Thermal coagulation and mechanical clipping** are more effective and sustained than injection therapy alone in terms of bleeding control, rebleeding and need for surgery (61,62).

Vascular ectasia

Argon Plasma Coagulation (APC) is useful for the treatment of a vascular ectasia (63).

Table 5. — **Forrest classification for the risk of rebleeding**

Endoscopic Stigmata	Forrest classification	Risk of rebleeding without treatment
Spurting bleeding	Ia	100%
Oozing bleeding	Ib	30%
Non bleeding visible vessel	IIa	50%
Adherent clot	IIb	30%
Flat spots	IIc	< 8%
Clean base	III	< 3%

Mallory-Weiss syndrome

Mallory-Weiss syndrome heals spontaneously in many cases, endoscopic therapy is occasionally necessary. When endoscopic treatment is needed, the same rules apply as for ulcer bleeding (61). The use of a duodenoscope may be very helpful in this setting (5-D).

Tumour

Endoscopic haemostasis for bleeding related to an UGI tumour is often a temporary measure. Permanent haemostasis is difficult in many cases due to diffuse bleeding and the unique solution is surgical resection if possible (64).

Dieulafoy's lesion

Bleeding from Dieulafoy's lesions (mainly located in the stomach and duodenum) can be controlled by endoscopic therapeutic procedures. Hemoclipping is more effective than injection therapy (65). A safe alternative is injection plus heater probe coagulation (66). Band ligation was successful in case series but there is a risk of perforation and delayed bleeding (contraindicated in the duodenum). Argon plasma coagulation has been used in a case series (67). Tattooing of the lesion with India Ink is helpful for locating the lesion in case of endoscopic retreatment or surgical wedge excision.

PPI continuation or administration after therapeutic endoscopy

In a large RCT - after therapeutic endoscopy - high-dose intravenous omeprazole (80 mg bolus IV, followed by 8 mg/hour for 72 hours) was shown to significantly decrease the rate of rebleeding by approximately 5 to 10% (35). The need for surgery was reduced non-significantly by approximately 3%. Mortality was significantly reduced only in patients with active bleeding or non-bleeding visible vessel. Similar results were obtained with esomeprazole (after therapeutic endoscopy : 80 mg bolus IV, followed by 8 mg/hour for 72 hours). An updated meta-analysis of RCT's which included 5792 patients (5), disclosed that PPI therapy after endoscopy (whether therapeutic or not) dramatically r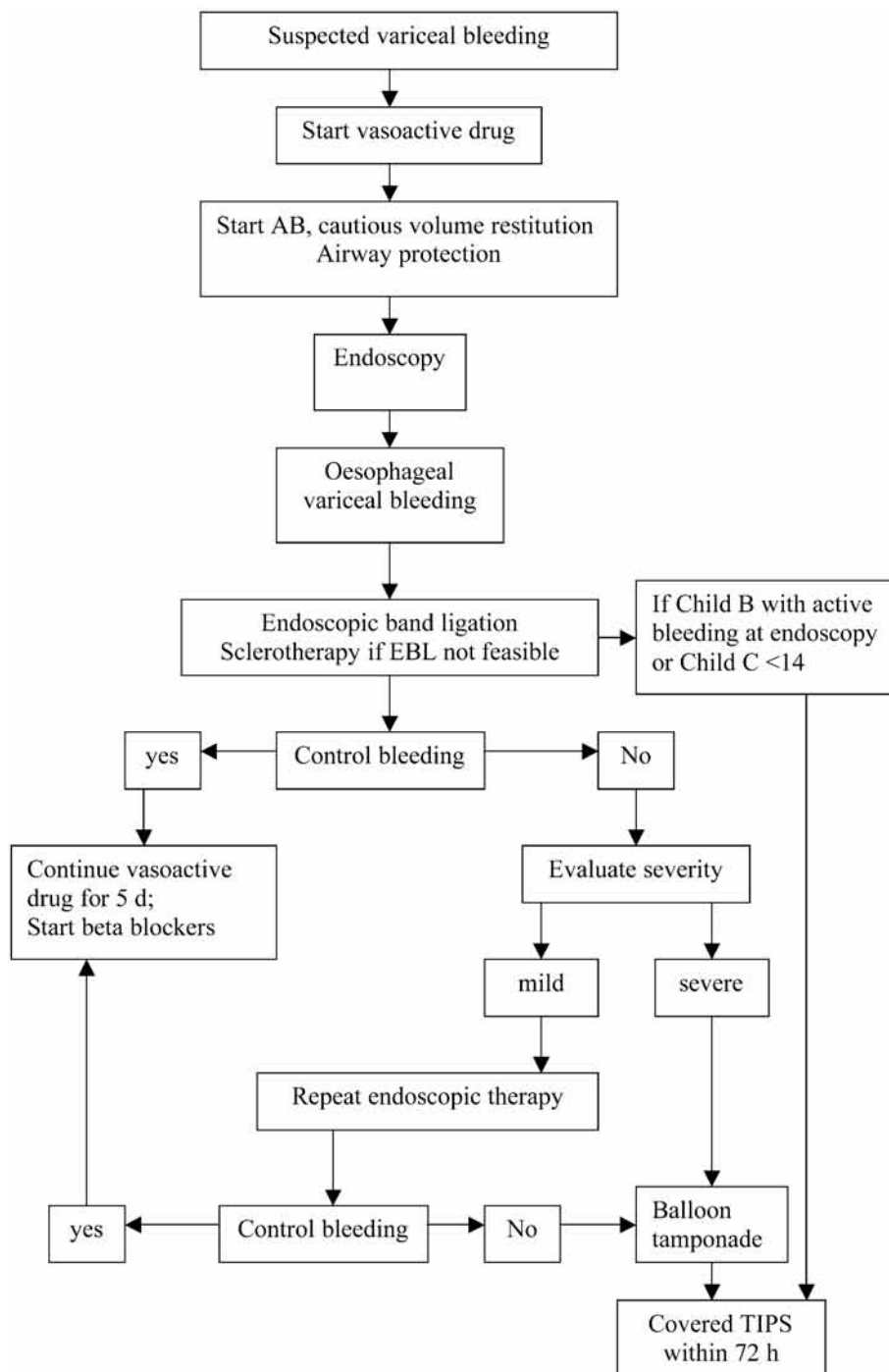educed the rebleeding rate (OR 0,45 CI : 0,36-0,57) and surgery (OR 0,56 CI : 0,45-0,70) but not mortality. A beneficial impact on mortality was only found in the subgroup of patients with active bleeding or non bleeding visible vessel who received haemostatic therapy and high dose IV PPIs for 72h (OR 0,57 CI 0,34-0,96). Lower doses of PPIs either IV or oral had no impact on mortality in this subgroup. As far as costs are considered for this strategy, high-dose IV PPI for high risk patients after therapeutic endoscopy appear more effective and less costly in Europe (68). However, the question of lower IV PPIs dose is still open (32).

Failure to control non-variceal bleeding : when should embolisation or surgery be considered ?

In patients in whom non-variceal bleeding cannot be controlled with a second endoscopic attempt, angiographic embolisation or surgery becomes the next therapeutic option. Where available, arteriography is an alternative option to surgery. This procedure can often obviate the need for surgery and is particularly useful for those unfit for surgery. Visualization of the bleeding vessel requires active bleeding at the time of arteriography at a rate of approximately 2 ml/min. Even though bleeding rate is not constant, angiography has a high probability of detecting an actively bleeding blood vessel if a patient is requiring more than 2 units of red blood packed cells per 4 hours to maintain a hemoglobin > 7 g/dL. The technical success of angiographic embolisation is above 90%, but prolonged clinical success is less at 65 to 70%. Early rebleeding will occur in approximately 20 to 30% of cases. The procedure has a low rate of major complications. In high-risk patients (APACHE II score > 16) mortality has been reported to be 23% versus 50% in patients treated with surgery. Transcatheter arteriography and intervention is the best treatment method for bleeding occurring into the biliary tree or pancreatic duct (69-72).

In the USA the use of surgery to control bleeding has decreased from 13.1% in 1993 to 9.7% in 2006. There has also been a significant decrease in the use of definitive surgery (vagotomy or resection). Surgery has a lower incidence of rebleeding than angiographic embolisation (72).

In conclusion, angiographic embolisation or surgery is indicated when arterial bleeding cannot be controlled

```
┌─────────────────────────────────┐
│   Suspected variceal bleeding   │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│      Start vasoactive drug      │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│  Start AB, cautious volume      │
│  restitution                    │
│  Airway protection              │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────┐
│    Endoscopy    │
└─────────────────┘
                │
                ▼
┌─────────────────┐
│  Oesophageal    │
│  variceal       │
│  bleeding       │
└─────────────────┘
                │
                ▼
┌──────────────────────────────────┐      ┌──────────────────────┐
│  Endoscopic band ligation        │─────▶│ If Child B with active│
│  Sclerotherapy if EBL not        │      │ bleeding at endoscopy │
│  feasible                        │      │ or Child C <14        │
└──────────────────────────────────┘      └──────────────────────┘
                │
                ▼
  ┌─────┐   ┌──────────────────┐   ┌─────┐
  │ yes │◀──│ Control bleeding │──▶│ No  │
  └─────┘   └──────────────────┘   └─────┘
     │                                 │
     ▼                                 ▼
┌──────────────────┐          ┌──────────────────┐
│ Continue         │          │ Evaluate severity│
│ vasoactive       │          └──────────────────┘
│ drug for 5 d;    │              │          │
│ Start beta       │              ▼          ▼
│ blockers         │          ┌──────┐   ┌────────┐
└──────────────────┘          │ mild │   │ severe │
     ▲                        └──────┘   └────────┘
     │                            │          │
     │                            ▼          │
     │             ┌──────────────────────┐  │
     │             │ Repeat endoscopic    │  │
     │             │ therapy              │  │
     │             └──────────────────────┘  │
     │                        │              │
  ┌─────┐  ┌──────────────┐ ┌─────┐  ┌──────────────┐
  │ yes │◀─│ Control      │▶│ No  │─▶│ Balloon      │
  └─────┘  │ bleeding     │ └─────┘  │ tamponade    │
           └──────────────┘          └──────────────┘
                                          │
                                          ▼
                                  ┌──────────────┐
                                  │ Covered TIPS │
                                  │ within 72 h  │
                                  └──────────────┘
```

Abbreviations : AB : antibiotic ; EBL : endoscopic band ligation ; TIPSS : transjugular intrahepatic portosystemic shunt.

Fig. 2. — Algorithm for oesophageal variceal bleeding (20, 21, 52) (Baveno V)

with endoscopy. In high risk patients, angiographic embolisation is preferred over surgery because of lower mortality (3-C).

Endoscopic treatment for PHT related bleeding

Oesophageal variceal bleeding (Fig. 2)

The **diagnosis** of an acute variceal bleeding is made upon the following criteria : active bleeding from a varix (oozing, spurting) ; presence of a "white nipple" fibrin clot overlying a varix (signature of variceal rupture) ; a clot on a varix ; the presence of varices without other potential source of bleeding and fresh blood in the stomach (12,21,73).

Endoscopic treatment should be performed at the time of diagnostic endoscopy (within 12 h after admission) by a skilled endoscopist and should always be used **in association with vasoactive treatment**, preferably
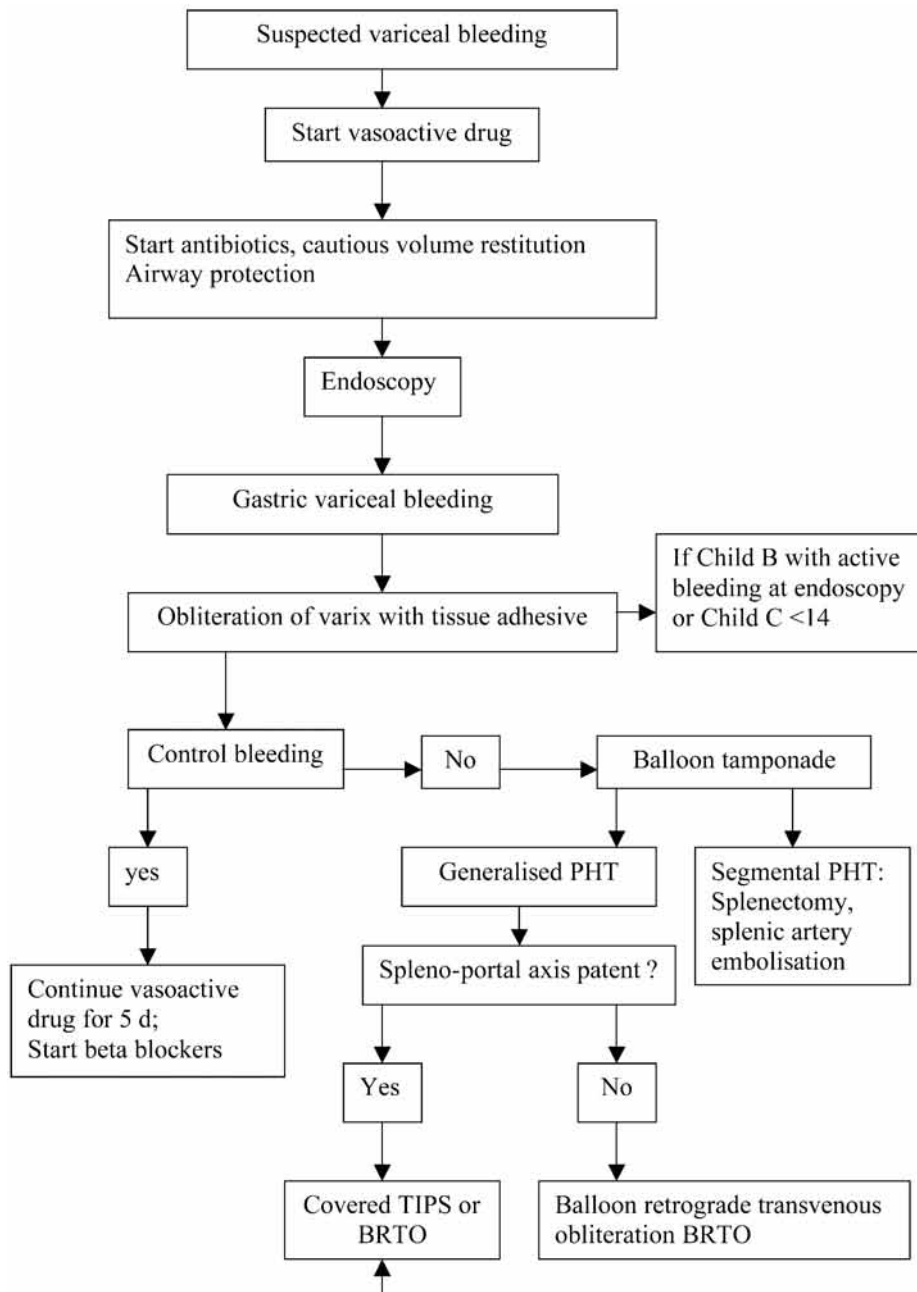
Abbreviations : BRTO : Balloon retrograde transvenous obliteration ; PHT : portal hypertension ; TIPSS : transjugular intrahepatic portosystemic shunt.

Fig. 3. — Algorithm for gastric variceal bleeding (52)

started before endoscopy (1a-A) (18,20). Both sclerotherapy and endoscopic band ligation (EBL) have shown to be effective in controlling oesophageal variceal bleeding. The Baveno IV and V guidelines are conclusive in their advice : **endoscopic band ligation is preferred** as this endoscopic therapy for oesophageal variceal bleeding is better for bleeding and rebleeding control and has less adverse events compared to sclerotherapy. Sclerotherapy can be accepted if EBL is not feasible, technically difficult or not available (1b-A) (12,18-21,23,51,74,75).

Endoscopic treatment for gastric variceal bleeding (Fig. 3)

Fundal varices account for 1-3% of variceal bleeds. The risk of gastric variceal bleeding is lower than oesophageal variceal bleeding, however the bleeding is more severe and mortality is higher (21). There are different types of gastric varices as shown in Figure 4.

Gastro-oesophageal varices type 1 are an extension of oesophageal varices along the lesser curvature and should be treated as oesophageal varices (18,52).
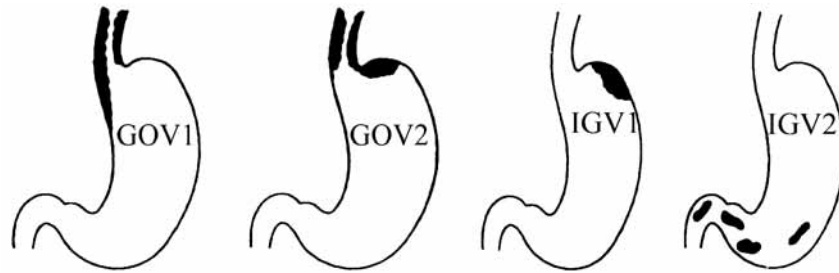
Fig. 4. — Different types of gastric varices :

GOV1 : gastro-oesophageal varices type 1 is an extension of oesophageal varices along the lesser curvature
GOV2 : gastro-oesophageal varices type 2 is an extension of oesophageal varices along the fundus
IGV1 : isolated gastric varices in the fundus
IGV2 : isolated gastric varices not in the fundus.

Endoscopic band ligation or tissue adhesives can be used (Baveno V) (20).

There are limited data for gastric variceal bleeding (from isolated gastric varices type 1 and 2 and gastro-oesophageal varices type 2) but the guidelines are quite uniform : variceal obliteration with a tissue adhesive (e.g. N butyl-cyanoacrylate, isobutyl 2 cyanoacrylate) is recommended and is more effective than EBL or sclerotherapy (1b-A) (18,20,51). Obliteration with a tissue adhesive has a better bleeding and rebleeding control, should be performed by an expert in endoscopy, can be difficult during active bleeding and complications (emboli) can occur (21,52).

If obliteration is not possible, transjugular intrahepatic portosystemic stent shunt (TIPSS) should be considered (1-B). Tamponade with a Linton balloon can be performed as a bridge to definite therapy (21,52). A Linton tamponade with 600 mL inflation is more effective than a Sengstaken Blakemore tamponade (52).
A second endoscopic attempt to stop gastric variceal bleeding is not indicated providing glue was used during the first session (21,52).

Treatment for portal hypertensive gastropathy

Portal hypertensive gastropathy (PHG) is supposed to cause less than 3% of acute bleedings. There are no RCT's assessing treatment for this cause of bleeding. Treatment is hypothetically based on decreasing gastric blood perfusion with vaso-active agents such as terlipressin or somatostatin (5-D) (52). Chronic bleeding from PHG can be treated with beta-blockers or TIPSS (52). Bleeding from PHT related jejunopathy should also be considered and assessed by capsule endoscopy (76,77).

Variceal bleeding from non cirrhotic portal hypertension or extrahepatic portal hypertension

Little literature about the treatment of variceal bleeding from non-cirrhotic portal hypertension is available. However the same endoscopic therapy for acute bleeding is advised as in cirrhotic variceal bleeding (2b-B). For secondary prophylaxis, endoscopic therapy is effective (2b-B). Decompressive procedures should be considered for patients with endoscopic failure (5-D) (18,20).

The place of TIPSS and Surgery in PHT related UGIB (Figure 1 and 2)

WHEN SHOULD COVERED TIPSS BE CONSIDERED ?

Polytetrafluoroethylene (PRFE)-covered TIPSS is extremely effective in controlling variceal (oesophageal and gastric) bleeding (control rates approaches 95%) and has a low risk of obliteration compared to non-covered stents. The goal of TIPSS placement is to reduce hepatic venous pressure gradient below 12 mmHg (3a-C) (78).

TIPSS is preferred above surgical shunts (3b-C) (78) and should be placed by an experienced interventional radiologist or a specially trained physician (5-D) (20,78). Sometimes retrograde embolisation of gastric varices may be required despite adequate decompression of portal venous system (3a-C) (78). TIPSS may decrease liver function capacity and cause encephalopathy (21).

EARLY TIPSS PLACEMENT

Two studies from Monescillo (79) and Garcia Pagan (80) show that high risk patients for rebleeding, have a survival benefit when early PTFE-covered TIPSS (within 72 h of admission) is placed compared to standard therapy (combined vasoactive treatment and band ligation) (1 year survival of 86% *vs*. 60%, respectively). Moreover, early TIPSS had a much lower rate of failure to control bleeding and of early rebleeding (3%) compared to combined vasoactive treatment and band ligation (50%) (80).

Based on these 2 studies, the recent Baveno V consensus meeting states that early covered TIPSS placement (within 72 h of admission) should be considered in patients at high risk for treatment failure. This is in patients with Child B cirrhosis and active bleeding at endoscopy and in Child C patients with < 14 points, after

medical and endoscopic treatment is installed (20). Reserving TIPSS as a rescue therapy after failure allows the patient sometimes to deteriorate to a point where survival is poor.

TIPSS AS SALVAGE THERAPY :

PTFE-covered TIPSS should be used as a salvage therapy in the following indications :
– if oesophageal and gastric variceal bleeding is not controlled with endoscopic and medical therapy
– when oesophageal variceal bleeding recurs despite 2 endoscopic attempts and full medical therapy (1-C) (12,51)
– if gastric variceal rebleeding occurs after a single failure endoscopy or if obliteration is not available (12,51,52).

TIPSS FOR OTHER INDICATIONS

TIPSS can also be recommended for recurrent bleeding from portal hypertensive gastropathy despite beta-blockade (4-C) (78). However, TIPSS is not useful for the treatment of bleeding from gastric antral vascular ectasia (GAVE) ("water melon stomach") (78).

SHUNT SURGERY FOR BLEEDING FROM PHT DUE TO INTRA-HEPATIC DISEASE (CIRRHOSIS MOSTLY)

Shunt surgery is extremely effective in controlling variceal bleeding (control rates approaches 95%), but due to worsening of liver function, mortality remains high. For this reason TIPSS is preferred above surgical shunts (3b-C) (78).

The ideal patient for surgical therapy is one with well preserved liver function who fails emergent endoscopic treatment and has no complications from the bleeding or endoscopy. The choice of surgery is usually dependent on the training and expertise of the surgeon.

SHUNT SURGERY FOR BLEEDING FROM PHT DUE TO PORTAL VEIN THROMBOSIS

Decompressive surgery or interventional radiological procedures should be considered for patients with portal vein thrombosis and failure of endoscopic therapy for bleeding (5-D). (Baveno 5) (20). The Sugiura procedure (oesophageal devascularisation) may be used in patients who are not candidates for a shunt operation such as those with extensive portal vein thrombosis with extension into the splenic and superior mesenteric veins.

Mesenteric-left portal vein bypass ("Rex bypass") is preferred in managing bleeding from pediatric patients with chronic extrahepatic portal vein thrombosis, if feasible (2b-B) (Baveno V) (20).

Failure to control PHT related bleeding

Definition of failure to control bleeding was defined in the Baveno guidelines IV and V (18,20) as fresh hematemesis ≥ 2 hours after the start of a drug treatment or therapeutic endoscopy ; a 3 g/dL drop in hemoglobin (≅ 9% hematocrit drop) if no transfusion is administered

or death. Failure to control bleeding implies a change in treatment options. TIPSS is the preferred strategy and should be placed within 24 hours.

Second-look endoscopy

The definition of a second-look endoscopy (also called scheduled repeat endoscopy) is an endoscopy scheduled within 24-72 h after the index bleed, without any clinical sign of rebleeding. However, the performance of second-look endoscopy remains controversial. In the published studies there are important differences in recruitment criteria, in definitions of recurrent bleeding, and important heterogeneity in the endoscopic therapies used, which all contribute to confound the effects of overall efficacy. In 3 RCT's either endoscopic injections or fibrin-glue in second endoscopy was used. Only one of these studies showed a marginal benefit in the reduction of recurrent bleeding with second-look endoscopy, and none showed any benefit on mortality or need for surgery. In 2 RCT's (both with small sample size) using thermal coagulation, a significant reduction in recurrent bleeding was obtained, but no effect on mortality (81,82). Most of the beneficial effects of a second-look endoscopy were published when injection therapy was used alone and when post endoscopy PPIs were not used. Therefore, currently, combination of endoscopic treatments and PPI administration really question the usefulness of a second look endoscopy (83). Based on the published data, the panel does not recommend routine second-look endoscopy, independent of the endoscopic technique used to stop the bleeding (1a-A).

However, a clinically meaningful and probably cost-effective strategy is to select high-risk patients for second-look endoscopy and retreatment, especially if the initial treatment is questionable (5-D). High-risk patients can be selected on the basis of the Glasgow Blatchford bleeding or Rockall score > 6 (1a-B) (see Table 2 and 3) (13-15).

Recurrent bleeding

Non-variceal rebleeding

Definition

Rebleeding is defined as clinical evidence of recurrent bleeding after a successful initial treatment. Risk factors associated with rebleeding are a past history of peptic ulcer bleeding, a history of smoking, presentation with hematemesis, hypovolemic shock before endoscopy, ulcer size > 2 cm and type of ulcer (84). The GBS and the Rockall scores are good indicators of rebleeding (Table 2 and 3). The use of post endoscopy PPIs dramatically reduces the rate of rebleeding from upper gastrointestinal lesions (see above).

Re-endoscopy with retreatment is mandatory, independently of the endoscopic technique used to stop the index bleed or the origin of bleeding (1a-A).

Failure to control non-variceal rebleeding

The same rules apply as for failure during the index bleed (see above).

Variceal rebleeding

Definitions

Significant rebleeding is defined by Baveno IV and V guidelines (18,20) as hematemesis or melena or a decrease of 3 g/dL hemoglobin if no transfusion is given after a successful initial treatment after the index bleed.

Failure to control bleeding implicates a change in treatment options.

Endoscopic retreatment and vasoactive medication (Figure 2 and 3)

If variceal bleeding is mild and the patient is stable, a second endoscopic therapy might be attempted for oesophageal varices. For gastric varices only 1 endoscopic attempt is allowed.

If it fails, or when bleeding is severe, the patient should be offered a derivative treatment (such as TIPSS described above) (85), before his clinical status further deteriorates.

Most patients have already received vasoactive medication for the treatment of the acute variceal bleeding and to prevent rebleeding. There are no studies showing that changes in vasoactive medications should be considered. However, the panel suggests, that increasing the dose to maximum levels allowed, could be beneficial (5-D).

Is there a place for balloon tamponade or oesophageal covered stents ? See B.14.

BALLOON TAMPONADE

Balloon tamponade is indicated for uncontrolled bleeding from oesophageal/gastric varices for whom a definitive therapy is planned within 24 h (1-B) (51). It is thus mostly used as a bridge to TIPSS or surgery. Balloon tamponade is effective in bleeding control (80%) but rebleeding after balloon deflation is high (50%). Complication rate (aspiration, migration, necrosis and perforation of the oesophagus) is high and associated with high mortality. The balloon should be released within 24 h to avoid necrosis of stomach/oesophagus. Linton tamponade (600 mL) can be used for oesophageal and gastric varices (52). Sengstaken Blakemore can only be used for oesophageal varices (5-D).

OESOPHAGEAL COVERED STENTS

A recent report suggests that oesophageal covered stents might achieve hemostasis in most patients with refractory oesophageal variceal bleeding, with the advantage over tamponade of less severe complications despite longer periods of treatment (12,20,21,53). RCT are ongoing. No statement concerning this treatment has been made during the Baveno V consensus meeting suggesting that further evaluation is needed (20).

This treatment is contra-indicated in case of suspected or obvious bleeding from gastric varices.

Upper GI bleeding follow up

Follow up of non-variceal bleeding patient

When should the patient be discharged from the ICU to the ward ?

Patients with an active bleeding or visible vessel can be safely discharged from the ICU to the ward after 1 day, if the patient is stable with no signs of rebleeding and if there is no other underlying pathology necessitating a longer stay in the ICU (5-D) (86).

When should the patient be discharged home ?

Patients without coexisting acute illnesses or bleeding disorders with clean-base ulcers can be discharged in the first day of admission (within 24 hours) (87). Patients with a Glasgow Blatchford score = 0 may even be managed as outpatients with elective endoscopy scheduled (16).

The length of hospital stay is often influenced by additional factors. As most of the rebleedings occur within 72 hours, 4 days could be an optimal hospital stay for patients with ulcers Forrest Ia-b or IIa and no other pathology. Other patients might be discharged after 3 days of hospitalization. Patients with a clean ulcer may be managed as outpatients (84).

Long term therapy

PPI TREATMENT

In case of a bleeding peptic ulcer, treatment with an oral PPI once a day is recommended for 6-8 weeks after treatment of the initial bleeding and achievement of hemostasis. Eliminating precipitating factors such as *Helicobacter pylori* (HP) and non steroidal anti-inflammatory drugs (NSAID's) is very important. Treatment of HP infection is more effective than anti-secretory therapy in preventing recurrent bleeding from peptic ulcers. Confirmation of infection (tests outside of the bleeding episode) and of eradication is required after HP treatment.

In case of concomitant acetyl salicylic acid or NSAID use, especially in high risk patients or patients with a history of NSAID-related gastric ulcer bleeding, co-therapy with a PPI is recommended to prevent ulcer recurrence on the long-term. In case of gastric ulcer, biopsies must be obtained to exclude underlying neoplasia.

After determining the cause of bleeding by endoscopy, specific therapy can be initiated. No studies are available comparing different dosages and duration of PPI treatment after endoscopic hemostasis of a bleeding ulcer, but the panel suggests that, if there is no rebleeding within 24 hours, the patient can be switched to an oral PPI 40 mg once a day for 1 to 2 months.

ERADICATION OF HP

Documentation of HP is advocated. Histology is preferred. HP should be eradicated in peptic ulcers showing positive results for this bacteria (88,89).

Triple therapy (PPI twice a day, clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 10-14 days, or PPI twice daily in combination with clarithromycin 500 mg twice daily and metronidazole 500 mg twice daily (penicillin allergic patients) can be used. Confirmation of HP eradication is required (88,89).

RESUMPTION OF ANTICOAGULANTS AND ANTIPLATELET DRUGS

Resumption of acetyl salicylic acid with concurrent PPI is superior to switching to clopidogrel alone for prevention of gastrointestinal bleeding in patients with acetylsalicylic acid-related disease (90). Available evidence suggests that treatment with a PPI is a useful precaution in patients with a recent history of gastrointestinal ulceration or bleeding that have to start with aspirin and/or clopidogrel (91,92).

Acetylsalicylic acid, as a prophylaxis of thromboembolic events, should be restarted as soon as possible, as withdrawal is associated with a 3-fold higher risk for major adverse cardiac events (93). According to the literature acetylsalicylic acid should be ideally resumed 1 or 2 days after endoscopy.

Recent studies have shown possible interaction between PPI's and clopidogrel. However, concomitant use of pantoprazole or esomeprazole did not have this effect and may be appropriate PPI's to be used in patients in whom there is a clear indication for clopidogrel (94,95). Clinical trials have shown that PPI's in standard doses significantly reduce the incidence of ulcers associated with the use of NSAID's (96).

Follow up of variceal bleeding patient

When should the patient with variceal bleeding be discharged from the ICU to the ward ?

Patients with variceal bleeding should always be managed at the ICU until the patient is stable.

The patient can be discharged when he is extubated ; has a good saturation with less than 5 L/min of oxygen ; is hemodynamically stable without vasopressors ; has a stable kidney function and has no signs of ongoing bleeding (5-D).

When should the patient with variceal bleeding be discharged to home ?

The highest risk of rebleeding is within 5 days, so the patients should receive pharmacological treatment for 5 days (20). Beta-blockade should be started around day 4 to have overlap with the vasoactive medication (target heart rate is 50-60/min) and when no evidence for acute variceal bleeding within 24 h exists (5-D).

The patient should be hemodynamically stable ; having a stable kidney function ; no active infections ; no

or minimal encephalopathy (5-D). The patient should have received a check up with ultrasound, Doppler ultrasound of the hepatic vessels and serum alpha fetoprotein level.

Secondary prophylaxis for variceal bleeding ?

Combination of beta-blockade with EBL is the preferred treatment (I-A) (20).

Non-selective beta-blockers should be given in a maximal tolerated dose, until the heart rate is between 50-60 beats per minute (1a-A) (18,20).

Endoscopic band ligation should be repeated every 1-2 weeks (inquiry during the Vth Baveno meeting revealed that most centres performed EBL every 2 to 4 weeks) until eradication (2 to 4 sessions needed mostly), then repeat endoscopy 1 to 3 months later, and then every 6 to 12 months (1-C) (12,51).

The Baveno V (2010) guidelines for secondary prophylaxis for variceal bleeding (20) are as follows :

– *In patients with cirrhosis*

The preferred therapy is beta-blockers + endoscopic band ligation (1a-A). Hemodynamic response assessment to drug therapy provides prognostic information about rebleeding risk and survival. Nitrates in combination with beta-blockers may improve hemodynamic response in non responders to beta-blockers alone (5-D).

– *In patients with cirrhosis who are unable or unwilling to be treated with endoscopic band ligation :*

Beta-blockers + nitrates may be the preferred option.

– *In patients who have contraindications or intolerance for beta-blockers* (Baveno V = IV) :

Band ligation is the preferred treatment for prevention of rebleeding (5-D) (20).

– *In patients who fail endoscopic and pharmacological treatment for prevention of rebleeding :*

Covered TIPSS is effective and is the preferred option. Surgical shunts (distal splenorenal shunt or 8 mm H-graft) are effective for patients with Child A/B cirrhosis (2b-B) ; it is an alternative if TIPSS is not available. Transplantation provides good long-term outcomes in Child C cirrhosis and should be considered (2b-B). TIPSS can be used as a bridge to transplantation (4-C).

– *Patients who bled from gastro-oesophageal varices type 1 (GOV1) :*

Can be treated with tissue adhesive, beta-blockers or band ligation (2b-B).

– *In patients who bled from gastro-oesophageal varices type 2 (GOV2) or isolated varices :*

Tissue adhesive (1b-A) or TIPSS (2b-B) are recommended.

– *In patients who bled from portal hypertensive gastropathy (Baveno IV = V)*

Beta-blockers should be used for prevention of recurrent bleeding (1b-A)

– *In patients in whom beta-blockers are contraindicated or failed and who cannot be managed by non-shunt therapy :*

TIPSS or surgical shunts should be considered (4-C) (Baveno IV = V)

Antibiotic (AB) prophylaxis after hospital discharge for variceal bleeding

In patients who have a variceal bleeding, AB prophylaxis should be started on admission as described above but should be given short term, mostly 7 days (20). When there is a confirmed infection (spontaneous bacterial peritonitis excluded) AB's should be given as usually until the infection is resolved.

When there was a spontaneous bacterial peritonitis present, secondary prophylaxis (oral norfloxacine 400 mg 1/d) should be given life long or until transplantation or until ascites resolves completely.

Long term follow-up of the cirrhotic patient

The cirrhotic patient should be screened for the development of hepatocellular carcinoma every 6 months with ultrasound and determination of serum alpha fetoprotein level.

An overview of the general management of non-variceal and variceal bleeding is proposed in Table 6 and 7.

Children's specific recommendations for the management of UGIB

Introduction

UGIB in children is uncommon but potentially life threatening. Due to its rarity, literature data on pediatric UGIB are scarce. Only one population based pediatric survey (in children from 2 months to 16 years of age) is available which was conducted in France (97). According to this study, the incidence of UGIB in children is 1-2/10,000 per year. The incidence of clinically significant UGIB in children admitted to the ICU has been reported to be 0.4-1.6% (98). In the French population study, the source of bleeding was an oesophageal lesion in 40%, a gastric lesion in 38% and varices in 5%. Upper gastrointestinal endoscopy was normal in 17% (97). In centres specialised in pediatric liver disease the proportion of variceal bleeding might be higher. The most frequent cause of life threatening UGIB, however, is variceal bleeding which in children, in contrast to adults, most often is related to extrahepatic portal vein obstruction (EHPVO).

Table 6. — **Management of NON-variceal bleeding**

		Level of evidence and Grade recommendation
General supportive care	Resuscitation	
	– Goal : MAP > 65 mmHg and/or SBP > 100 mm/Hg	5 - D
	– Volume expander : Cristalloids	5 - D
	– Vasopressors for persistent hypotension Noradrenaline	5 - D
	– Transfusion of blood products : packed red blood cells to reach Hb of 8 g/dL (9-10 g/dL if coronary or cerebrovascular disease)	1 - B
	– Intubation and sedation ongoing hematemesis, hemodynamic instability, alteration in mental status	5 - D
	– Transfer to ICU if Glasgow Blatchford bleeding score > 8 or GCS < 8	2 - B
Vasoactive medication	Not recommended	1 - B
Proton pump inhibitors (PPI)	Indicated BEFORE and AFTER endoscopy (40 mg IV bid or continuous infusion for 72 h depending on severity)	1 - A
Antifibrinolytic medication	No indication	1a - A
Antimicrobial prophylaxis	No indication	5 - D
Coagulation factors	FFP and platelets : no evidence prior to endoscopy Platelets transfusion if count < 30,000/mL	5 - D 5 - D
Pharmacologic stomach cleansing (erythromycin)	Indicated	1 - A
Endoscopy	Indicated within 24 h of admission Earlier if GBS > 8	1 - A 5 - D
Helicobacter pylori eradication	Mandatory	1 - A

Table 7. — **Management of variceal bleeding**

		Level of evidence and Grade recommendation
General supportive care	Resuscitation	
	– Goal : MAP > 65 mmHg and/or SBP > 100 mm/Hg	5 - D
	– Volume expander : Albumin 5%	5 - D
	– Vasopressors for persistent hypotension Noradrenalin or Terlipressin	5 - D
	– Transfusion of blood products : packed red blood cells to reach Hb of 8 g/dL (9-10 g/dL if coronary or cerebrovascular disease)	1 - B
	– Intubation and sedation ongoing hematemesis, hemodynamic instability, alteration in mental state	5 - D
	– Transfer to ICU if Glasgow Blatchford bleeding score ≥ 8	2 - B
Vasoactive medication	Before endoscopy – Terlipressin bolus I.V. : 1 – 2 mg according to weight followed by bolus 1-2 mg/4 h or continuous infusion 6 mg/day for 48 h then 1 mg/4 h until day 5 – Somatostatin bolus I.V. (5 min) 250 μg followed by continuous infusion 6 mg/day (if active bleeding at endoscopy 12 mg/day)	1b - A
Proton pomp inhibitors (PPI)	No evidence in variceal bleeding	
Antifibrinolytic medication	No indication	1a - A
Antimicrobial prophylaxis	– After blood, ascites and urine cultures – Amoxicillin – Clavulanic acid or third generation cephalosporins or Quinolones according to local resistance - Maximum 7 days	1a - A
Coagulation factors	FFP and platelets : no evidence prior to endoscopy	5 - D
	Overtransfusion of FFP and platelets increase portal pressure and bleeding	2b - B
	Platelets transfusion if count < 30,000/mL	5 - D
Endoscopy	Timing : as soon as possible (< 12 hours)	5 - D
TIPSS	Early (< 72 h) for patients with Child B and active bleeding at endoscopy or Child C (< 14 points)	

As UGIB in children is rare, RCT's on the management of UGIB are lacking. Many treatment strategies are deducted from the management of UGIB in adults and similar evidence-based approaches do not exist as it comes to pediatric UGIB. In the following paragraphs, some specificities and differences in the approach to UGIB in children compared to adults will be highlighted.

General Management

Initial management and resuscitation

The initial treatment focuses on maintenance of the airway and provision of adequate oxygenation and ventilation followed by cardiovascular resuscitation. The first step is the immediate differentiation between a hemodynamically stable child and a child in hypovolemic shock. In children age-adjusted tachycardia is the most sensitive indicator of severe blood loss, whereas blood pressure may initially be maintained due to important vasoconstriction in hypovolemic children. Hypotension and delayed capillary refill indicate the necessity of immediate intervention as these are signs of severe hypovolaemia (> 25% blood loss) and they precede collapse (Table 8).

In case of hypovolemic shock we refer to the official European Pediatric Life Support guidelines for the management of hypovolemic shock in children.

Airway protection is always necessary in case of hemodynamic instability, neurological deterioration (agitation, GCS < 8, deterioration of the level of consciousness), respiratory distress and ongoing bleeding. It is also recommended when dealing with infants, in case of signs of severe bleeding (> 20% loss of blood volume), recurrent vomiting and need for invasive procedures (e.g. central venous access, endoscopy).

In a hemodynamically stable child, as in adults, blood volume reconstitution should be done cautiously and

Table 8. — **Normal vital signs, heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure according to children's age**

AGE	HR at rest (/min)	RR at rest (/min)
Newborn	120-160	30-60
1-6 months	120-150	30-50
7-12 months	110-140	25-40
1-3 months	90-130	20-30
4-5 years	85-120	20-25
6-12 years	70-100	16-22
13-18 years	60-80	12-18

AGE	Systolic blood pressure (mmHg)	
	Normal	Lower limit
0-1 months	> 60	50
1-12 months	> 80	70
1-10 years	90 + [2 × age in years]	70 + [2 x age in years]
> 10 years	110-130	90

Diastolic blood pressure = 0.5 to 0.66 × systolic blood pressure.

conservatively to maintain hemodynamic stability but to avoid overcorrection which can maintain the bleeding. The amount of blood transfused should be adjusted to the age and weight of the child aiming for a hemoglobin (Hb) concentration of 8 g/dL which can be calculated using the following formula : (target Hb concentration – observed Hb concentration) × 3 × weight of the child in kg.

Cholestatic and/or breastfed infants are at risk for hemorrhagic disease of the newborn due to vitamin K deficiency. The latter should always be suspected in infants presenting with UGIB and prompt administration of IV vitamin K is required.

The cause of severe life threatening UGIB in children is most frequently bleeding from varices but on rare occasions aorto-oesophageal fistula, Dieulafoy lesion, or ulcers can also be the cause.

Two major categories of UGIB in children should be differentiated :

1. Mucosal erosion or ulceration : ask for use of NSAID (97), abdominal pain, foreign body ingestion, vomiting, stress factors.
2. Variceal bleeding : look for any clinical signs of liver disease or a neonatal history of umbilical catheters. An extrahepatic portal vein obstruction, however, often first presents with a severe bleeding episode in an otherwise perfectly healthy child without any previous history of note.

Some limited blood tests can be helpful in the differential diagnosis and the assessment of the severity of the UGIB : Hb and platelet counts, clotting and liver function tests.

Hospitalisation

Referral to a tertiary care centre where a multidisciplinary team of pediatric intensivists, pediatric gastroenterologists and pediatric surgeons is available is indicated in the following circumstances : important UGIB with drop in Hb level, (suspicion of) variceal bleeding and recurrent bleeding. Since early endoscopy is indicated, transfer should be organized as soon as possible once the child has been stabilised.

Initial medical treatment

The empiric use of acid-suppressive medication in children is justified based on the predominance of peptic causes of UGIB. In children, clear evidence is lacking (only uncontrolled trials and case reports are available) regarding a possible superiority of PPI's compared to H2-blockers (99).

PPI's : In children most data are available for the oldest molecule : omeprazole. The clearance of omeprazole in children is influenced by age with a slower metabolism in infants below 10 days of age, an increased metabolism between the age of 1 and 6 year and comparable metabolism to adults thereafter (40,100,101). Further on, CYP2C19 activity as well as the presence of systemic inflammatory response will alter the clearance of omeprazole (102). The recommended doses of IV omeprazole vary from 1 mg/kg once daily to 0.5 mg/kg twice daily to 40 mg/1.73 m² in order to maintain the gastric pH above 4 (99,103,104).

H2-blockers : The dose of ranitidine needed to maintain pH above 4 in children is age dependent. Preterm infants need 0.5 mg/kg IV twice daily, whereas term infants need 1.5 mg/kg IV three times a day and children need 1.5 mg/kg IV four times a day (105,106).

There are no pediatric data on the duration of IV acid-suppressive therapy.

Vaso-active drugs : Based on adult data and because the use of vaso-active medication has been proven to be safe in children, it is recommended to use vaso-active drugs as soon as possible before diagnostic endoscopy in children suspected of variceal bleeding (107). However, there is a lack of controlled trials in children.

In Belgium, in pediatric practice, the most frequently used vaso-active drug is somatostatin (starting bolus 3.5 µg/kg IV over 5 minutes, followed by 3.5 µg/kg/h) (98). In analogy with adults, based on the Baveno V guidelines, treatment duration of 5 days is empirically recommended.

Endoscopy

Indication for endoscopy

An endoscopy can only be performed in a hemodynamically stable child, under general anesthesia with size adapted material by an experienced endoscopist.

Endoscopy in young children is more challenging compared to adults : the endoscope can cause pressure on the trachea, furthermore ventilation problems due to gastric dilatation by insufflated air occur more frequently. An experienced pediatric anaesthetist or pediatric intensivist is therefore required during the procedure.

Indications for early endoscopy are not standardised. There are no pediatric studies comparing early endoscopy with conservative management nor has the risk of re-bleeding been assessed. Endoscopy in children seems, however, as safe as in adults when performed by experienced endoscopists (108). Endoscopy is mandatory when blood transfusion is required or in case of unexplained recurrent bleeding (109). Endoscopy should be carried out as soon as possible in a stable patient (within 12-24 hours, preferably even in a shorter time period). Immediate endoscopy is indicated in case of early failure to control bleeding (107).

Endoscopic treatment of varices

Based on adult data, antimicrobial prophylaxis directed at the intestinal flora (second or third generation cephalosporins) is recommended in children with variceal bleeding (107).

Sclerotherapy or EBL are as effective in the control of acute bleeding in children (107). One RCT in 49 children with EHPVO demonstrated that band ligation achieved variceal eradication more quickly with a lower re-bleeding rate and fewer complications compared to sclerotherapy (110). However, the choice of which type of endotherapy to use should be determined by local expertise and technical considerations (107). A specific concern regarding EBL of oesophageal varices in small children is the difficulty to pass the loaded apparatus through the pharynx and the risk of iatrogenic oesophageal damage. In small children in whom the adult multiband ligator does not pass, a small size multiband ligator adapted for an 8.5 mm endoscope can be used.

As in adults, acute gastric variceal bleeding can be controlled using tissue adhesive (e.g. N-Butyl-Cyanoacrylate) (111), but carries a small risk of acrylate dislocation causing (cerebral) thrombosis.

Balloon tamponade is a rarely used rescue therapy in uncontrolled bleeding in children. Experience is very limited and it should only be used for less than 24 hours on a pediatric ICU in experienced hands. In very small children, Foley urinary catheters or oesophageal balloon dilators can be used instead of the classic Sengstaken Blakemore or Linton tube.

Endoscopic treatment of non-variceal bleeding

As in adults, ulcers are the most frequent cause of non-variceal bleeding. If the size of the child permits the use of adult material the same techniques can be applied in children. However, published experience is limited to case reports (112-114). In case of infants, the narrow

operating channel of the pediatric scope (2 mm) may limit the treatment options to Argon plasma coagulation and injection techniques.

In any case of severe UGIB surgical backup should be available as the blood volume of a child is only 65-80 mL/kg.

There are no data on the need for a second look endoscopy after endoscopic treatment of non-variceal bleeding in children. As in adults, in selected high risk patients this can be an option, especially when initial treatment is questionable.

Recurrent bleeding

Recurrent variceal bleeding

Failures of initial therapy with combined pharmacological and endoscopic approach are best managed by a second attempt at endoscopic therapy. In case of persistent bleeding, shunt procedures are indicated.

The experience with TIPSS is limited in children. The procedure is technically more challenging (particularly in children with biliary atresia due to periportal fibrosis and small portal veins) and often considered as a bridge to transplantation (115). Where possible PTFE covered stents should be used.

As extrahepatic PHT is more common in children than in adults, the majority of these young patients are good candidates for surgical shunt procedures. When feasible the meso-Rex shunt is preferred (116-118). Excellent results with portosystemic shunts have been described in children especially with the distal splenorenal shunt (119).

Recurrent non-variceal bleeding

There are no data on the recurrence rate or risk factors of non-variceal bleeding in children. As in variceal bleeding a second attempt at endoscopy combined with pharmacological therapy is advised.

Follow up

Follow up after variceal bleeding

Band ligation therapy has been shown to be effective in children with PHT and may be superior to sclerotherapy when feasible (120). There are no specific pediatric recommendations about the frequency of endotherapy in follow-up and eradication of varices in children. Therefore we refer to the adult BavenoV guidelines.

The use of β-blockade as either replacement or additional therapy for band ligation in children requires further investigation. In children, there is an important theoretical concern that, by limiting tachycardia, non-selective β-blockers may impair tolerance of hypovolaemia and worsen the outcome from variceal hemorrhage (121). It is likely that post-pubertal teenagers will respond to β-blockers and bleeding like adults whereas

these concerns apply primarily to infants and younger children. Age may therefore be an important factor in the decision to prescribe β-blockers. In most studies, the dose of the β-blocker is adjusted until the heart rate is reduced to 75% of its baseline value (120). To achieve this, most children require a dose between 1 and 2 mg/kg/d. Unfortunately, there are no pediatric data to describe the splanchnic hemodynamic response to β-blockade or the optimum dosage schedule which gives maximum efficacy and minimum risk.

Follow-up after non-variceal bleeding

There are no studies on the duration of PPI treatment after bleeding. There are some case series investigating healing of oesophagitis due to gastro-oesophageal reflux in children. In 80% endoscopic healing is observed after 4 weeks of treatment and in 98% after 102 day (103, 121,122). The wide range of healing time might support the advice to endoscopically check ulcer healing before stopping treatment in case of a non-variceal UGIB.

Due to the high omeprazole clearance in children aged 1 to 6 years, the therapeutic doses needed to obtain healing vary from 0.7 to 3.5 mg/kg/day (100,122). In case of the presence of HP infection, triple treatment regimens containing 2 antibiotics and a PPI, are advised for eradication (123).

Conclusions

The current guidelines for the management of UGIB include recommendations for the diagnostic process, general supportive care, pharmacological therapy aiming at bleeding control, specific and endoscopic treatment of acute bleeding and follow-up for both gastro-duodenal ulcers and portal hypertension induced bleeding. These guidelines were made for pediatric and adult patients, however, for pediatric patients there are more expert opinion guidelines then EBM based guidelines.

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