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REVIEW

Diagnosis and therapy of non-variceal upper gastrointestinal bleeding

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Abstract

Non-variceal upper gastrointestinal bleeding (UGIB) is defined as bleeding proximal to the ligament of Treitz in the absence of oesophageal, gastric or duodenal varices. The clinical presentation varies according to the intensity of bleeding from occult bleeding to melena or haematemesis and haemorrhagic shock. Causes of UGIB are peptic ulcers, Mallory-Weiss lesions, erosive gastritis, reflux oesophagitis, Dieulafoy lesions or angiodysplasia. After admission to the hospital a structured approach to the patient with acute UGIB that includes haemodynamic resuscitation and stabilization as well as pre-endoscopic risk stratification has to be done. Endoscopy offers not only the localisation of the bleeding site but also a variety of therapeutic measures like injection therapy, thermocoagulation or endoclips. Endoscopic therapy is facilitated by acid suppression with proton pump inhibitor (PPI) therapy. These drugs are highly effective but the best route of application (oral *vs* intravenous) and the adequate dosage are still subjects of discussion. Patients with ulcer disease are tested for *Helicobacter pylori* and eradication therapy should be given if it is present. Non-steroidal anti-inflammatory drugs have to be discontinued if possible. If discontinuation is not possible, cyclooxygenase-2 inhibitors in combination with PPI have the lowest bleeding risk but the incidence of cardiovascular events is increased.

Key words: Gastrointestinal bleeding; Gastric ulcer; Duodenal ulcer; Endoscopy; Endoscopic therapy

Core tip: Non-variceal upper gastrointestinal bleeding (UGIB) is still accompanied by a significant mortality rate in older patients. Causes of UGIB are ulcers, Mallory-Weiss lesions, erosions, esophagitis or angiodysplasia. Endoscopy offers the localisation of the bleeding site as well as a variety of therapeutic measures. Patients with peptic lesions are effectively treated with proton pump inhibitors. *Helicobacter pylori* is a risk factor for the genesis of peptic ulcers and eradication therapy should be given if it is present.

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INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is defined as bleeding proximal to the band of Treitz. Approximately 10% to 20% of bleeding episodes are from esophageal, gastric or duodenal varices or from portal hypertensive gastropathy related to portal hypertension. This article will deal only with non-variceal UGIB. Table 1 gives an overview of possible causes of UGIB.

The reported annual incidence of UGIB ranges from 48 to 160 cases per 100000 adults[1-6], with a mortality from 10% to 14%[4,7]. Besides the advances in endoscopy and intensive care medicine, these mortality rates have not changed very much during the last decades[3,4,7]. Most likely, this is caused by the fact that patients with UGIB are nowadays older and more likely to have relevant co-morbidity than in the past. Accordingly, the mortality rate in patients under the age of 60 years and no relevant co-morbidity is almost zero[8].

Clinical signs of UGIB are vomiting of blood (haematemesis) and/or passage of black, tarry stools (melena). In some cases, melena might be caused by bleeding from the small intestine downwards the duodenum. Tarry stools are usually seen if more than 50 mL to 100 mL of blood is lost per day. The passage of bright red blood per rectum (haematochezia) could be caused by severe, brisk bleeding. Non-specific signs like fatigue, prostration or shortness of breath could be caused by occult bleeding. Typical laboratory findings are anaemia, low MCV, low ferritin and an increase in the reticulocyte count. Patients are haemodynamically affected (hypotension, tachycardia) if more than 10% to 20% of the total intravascular blood volume is lost. Several clinical signs provide clues to the localisation of the bleeding: Melena and/or haematemesis indicate UGIB. Haematochezia indicates lower gastrointestinal bleeding or massive bleeding in the upper GI-tract, typically distal of the pylorus. Ascites and/or jaundice make the diagnosis of liver cirrhosis very likely and point at variceal bleeding. Special attention should be paid to the medical history of the patient: Non-steroidal anti-inflammatory drugs (NSAID) or acetyl-salicylic acid (ASA) make bleeding from ulcers or severe erosive gastritis likely. The presence of an aortic prosthesis increases the risk of an aorto-intestinal fistula.

Patients who present with signs and symptoms of UGIB should first be stratified into low or high risk[8,9] to guide further treatment. The stratification is done on the basis of clinical, endoscopic and laboratory criteria using prognostic scales. The most used scores in clinical practice are the Blatchford *et al*[10] and Rockall *et al*[11] scores. Tables 2 and 3 give a concise overview of the two scores. Both scores allow the identification of patients with low risk, meaning that these patients do not require emergence endoscopy and could safely be managed as outpatients. Clinical criteria include pulse, blood pressure, melena, cardiac failure, syncope and evidence of liver disease. Placement of a naso-gastric tube and aspiration of blood make the diagnosis of an acute bleeding very likely. Haemoglobin and blood urea levels are laboratory criteria.

Every patient who is haemodynamically instable should first be stabilized in an intensive care-unit before endoscopic diagnostic or therapy is initiated.

The risk of re-bleeding is based on the Forrest classification[12] (Table 4) and endoscopic findings like the localisation of the bleeding and type of bleeding (ulcer, cancer or variceal bleeding).

BLOOD TRANSFUSION

In contrast to immediate and sufficient volume resuscitation, the timing and amount of blood transfusions in patients with UGIB is a subject of intense discussion. It is widely accepted that patients with a haemoglobin level of 7 g/dL or less should receive a transfusion, whereas it is rarely indicated in patients with a haemoglobin level of 10 g/dL or more. The threshold for each patient has to be individually defined and depends on factors like age, haemodynamic status, markers of tissue hypoxia and presence of coronary artery disease. A meta-analysis of studies in a heterogeneous group of critically ill patients (trauma, surgery, intensive care)[13] showed that transfusion was associated with an increase in mortality, multi-organ failure as well as an increase in nosocomial infection and acute respiratory distress syndrome. Yet, confounding factors of this meta-analysis by the need for transfusion itself could not be excluded.

Most national[8] and international guidelines[14,15] on UGIB recommend a target level for blood transfusions in patients without signs of tissue hypoxia and/or coronary artery disease in the range of 7 g/dL to 9 g/dL. This was confirmed by a trial in critical care patients that demonstrated a lower mortality in patients with a haemoglobin level of 7 g/dL to 9 g/dL compared to patients with a haemoglobin level of 10 g/dL to 12 g/dL[16]. However, in the context of UGIB the study has to be interpreted with caution since patients with UGIB were excluded in this study. A lower mortality in patients with UGIB and a restrictive transfusion regimen (haemoglobin below 7 g/dL *vs* haemoglobin below 9 g/dL) was shown in a recent trial including 921 patients[17]. In patients with massive bleeding the haemoglobin level is of limited use only, since there is no time for haemodilution and a drop in haemoglobin concentration to develop. Therefore, patients with massive bleeding should be managed with transfusion of blood, platelets, clotting factors and volume resuscitation according to local protocols for managing massive bleeding.

Table 1 Causes of upper gastrointestinal bleeding

Peptic ulcer	
Oesophagitis	
Drug-induced mucosal damage (NSAID)	Ulcer
	Erosion
Traumatic or postoperative lesions	Mallory-Weiss lesion
	Arterio-intestinal fistula
Malignant tumor	
Sequelae of portal hypertension	Oesophageal varices
	Varices of the gastric fundus
	Portal hypertensive gastropathy
Vascular anomalies	Dieulafoy lesion
	Gastric antral vascular ectasia (GAVE syndrome)
	Angiodysplasia
	Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia)
Bleeding from the hepato-pancreatico-biliary system	
Bleeding from a duodenal diverticulum	

NSAID: Non-steroidal anti-inflammatory drugs.

Table 2 Glasgow-Blatchford Score[10]

Admission risk marker	Score component value
Blood urea (mmol/L)	
6.5-8.0	2
8.0-10.0	3
10.0-25	4
> 25	6
Haemoglobin (g/dL) for men	
12.0-12.9	1
10.0-11.9	3
< 10.0	6
Haemoglobin (g/dL) for women	
10.0-11.9	1
< 10.0	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
< 90	3
Other markers	
Pulse ≥ 100 (per minute)	1
Presentation with melaena	1
Presentation with syncope	2
Liver disease	2
Cardiac failure	2

The Blatchford score has to be used before endoscopy. The score component values are added up for each component. A score of 0 is the cut-off with any patient scoring > 0 at risk of requiring an intervention.

ANTICOAGULATION

A reasonable amount of patients with UGIB is on a medication with anticoagulants, but data from clinical trials that investigated correction of an underlying coagulopathy is sparse. A retrospective study was not able to show that patients with a baseline international normalized ratio (INR) greater than 1.3 had a higher risk of re-bleeding, surgery or mortality[18]. These findings were substantiated by another study[19], in which neither platelet count nor INR predicted re-bleeding. In contrast to these findings, one study, published in abstract form only, showed that an INR of 1.5 or greater at presentation is a predictor of mortality[20]. Correction of coagulopathy to an INR of less than 1.8 led to a lower mortality compared to a historical control group[21] without differences in time to endoscopy and units of transfused blood. Another study that compared cohorts of patients that underwent endoscopic treatment was not able to show differences in mortality, re-bleeding or need for surgery between patients on warfarin whose INR was corrected using fresh frozen plasma compared to patients without correction of coagulopathy[22]. The recommendation for clinical practice is that coagulopathy should not delay early endoscopic treatment and that coagulopathy should be corrected to an INR of 1.5 or less to facilitate endoscopic treatment. Correction of coagulopathy is best done by the application of prothrombin complex[23]. In patients on warfarin therapy, iv Vitamin K should be administered. The situation is even more complicated by the fact that an increasing amount of patients is on a therapy with target-specific oral anticoagulants like rivaroxaban or epixaban. Antidotes or specific reversal agents for these drugs are lacking. The INR is of no value in target-specific oral anticoagulants and correction of coagulopathy using prothrombin complex on the basis of the clinical needs and judgement is necessary[24].

Platelet transfusion is not necessary in patients who are haemodynamically stable and have no signs of active bleeding. In contrast, patients with active bleeding and a platelet count of less than 50 G/L should receive platelets[8]. A substantial gap in evidence still remains in the case of massive bleeding. At the moment, there are no high-quality trials on the effect of component therapies and the ratio of red blood transfusion to component therapies or therapy with recombinant factor VIIa[25].

TIMING OF ENDOSCOPY

Endoscopy is able to identify the bleeding site in more than 80% of patients. It is the principle diagnostic tool in UGIB and haemostatic therapy could be applied. While diagnostic endoscopy in clinically stable patients without relevant co-morbidity is safe, complications may arise in actively bleeding patients with co-morbidities. Therefore, patients should be sufficiently stabilized before endoscopy is performed[8,15].

Several studies investigated the best time point for endoscopy in patients with suspected UGIB. Endoscopy within the first 24 h (early endoscopy) improves outcomes of high-risk patients and allows for early discharge of low-risk patients[9,26]. Only in a minority of high-risk patients endoscopy should be delayed due to reasons that make endoscopy an additional risk factor (*e.g.*, perforation, acute coronary syndrome). Endoscopy within 24 h after presentation was performed in the majority (> 75%) of patients in a US-study[27], whereas

Table 3 Clinical (pre endoscopy) and full (post endoscopy) Rockall score[11]

Variable	Score 0	Score 1	Score 2	Score 3
Age	< 60	60-79	≥ 80	
Shock	No shock	Pulse ≥ 100 Systolic blood pressure ≥ 100	Systolic blood pressure < 100	
Co-morbidity	Non major		Chronic heart failure, ischemic heart disease, major comorbidity	Renal failure, liver failure, metastatic cancer
Diagnosis	Mallory-Weiss lesion	All other diagnoses	GI malignancy	
Evidence of bleeding	None		Blood, adherent clot, visible or spurting vessel	

The first three rows make up the clinical score. After endoscopy the scores from the last two rows are added to create the full score. Scores are additive. A score of 0 for the clinical and scores from 0-2 for the full score are the clinical cut-offs to indicate patients at low risk of re-bleeding or death. GI: Gastrointestinal.

Table 4 Forrest classification[12] and the risk of re-bleeding within 24 h after exclusively medical therapy

	Re-bleeding risk (%)
Acute bleeding	
Forrest Ⅰ a (spurting bleeding)	90
Forrest Ⅰ b (oozing bleeding)	50
Signs of recent bleeding	
Forrest Ⅱ a (visible vessel)	25-30
Forrest Ⅱ b (adherent clot)	10-20
Forrest Ⅱ c (flat pigmented haematin on ulcer base)	7-10
Lesions without active bleeding	
Forrest Ⅲ (lesions without signs of recent bleeding or fibrin-covered clean ulcer base)	3-5

in a study from the United Kingdom[28] only half of the patients received endoscopy within the first 24 h. Early endoscopy is considered safe and effective in the vast majority of patients and is associated with a reduction in the length of hospital stay in patients of all risk groups[29-35]. A cohort analysis[28] showed a relevant trend (however not statistically significant) that the availability of after-hour endoscopy decreased mortality. These results are substantiated by findings that patients with UGIB who were admitted on weekends had higher in-hospital mortality[29]. However, a more recent study from the United Kingdom was not able to show a higher mortality in patients who were admitted on weekends[36]. Whereas these findings are in favour of early endoscopy within 24 h after presentation, a meta-analysis found no difference in mortality, reduction in re-bleeding or surgery comparing very early endoscopy (< 12 h) over early endoscopy (> 24 h)[15]. One study analysed the need for transfusions and length of hospital stay in patients with blood in the gastric tube aspirate and time to endoscopy < 12 h or > 12 h[33]. They found less need for blood transfusions and shorter hospital stay in the patients who underwent endoscopy in the first 12 h after presentation. Most likely the conflicting results in the available studies are due to the heterogeneity of the included patients. A study identified independent predictors for the need of endoscopy within 12 h after presentation[37]: Fresh blood in the gastric tube aspirate, hemodynamic instability, haemoglobin below 8 g/dL and a leukocyte count of more than 12 G/L. The recommendation from the available data is that patients with suspected UGIB should undergo endoscopy within 24 h after presentation. Patients who are hemodynamically instable and/or blood in the naso-gastric tube aspirate should undergo endoscopy immediately after resuscitation, at least within 12 h after presentation.

MEDICAL TREATMENT

The rationale for an acid suppressing therapy is to increase intra-gastric pH and to achieve stabilization of the blood clot that plugs the vessel defect and to promote ulcer healing. Whereas proton pump inhibitors (PPI) therapy is well tolerated and side effects in the acute, short-term use are rare, it is questionable if all patients that present with haematemesis or melena actually need PPI-therapy, since approximately 80% of ulcers stop bleeding without any form of intervention and re-bleeding is rare.

While the debate whether pre-endoscopic PPI-treatment is cost-effective or not[38-40] is ongoing, it is advisable in situations where endoscopic treatment is delayed or endoscopic expertise is not sufficient.

The effect of pre-endoscopic treatment with PPI was investigated in several trials and summarized in a Cochrane analysis[41] that was later updated by additional studies[42]. Of the included studies, one used an oral PPI regimen whereas the remaining five studies investigated iv PPI treatment. The meta-analysis was not able to show differences in re-bleeding, surgical intervention or mortality between the patients on PPI-treatment and patients in the control group. Nevertheless, the patients in the treatment group had less high-risk stigmata and need for endoscopic treatment.

The use of PPI therapy in patients with UGIB was investigated in numerous studies. A Cochrane analysis from 2006[43] as well as an update of this meta-analysis[44] comprising 24 and 31 randomized controlled trials (RCTs), respectively, studied PPI-treatment. Therapy with PPI - alone or in combination with endoscopic treatment - compared to placebo or histamine receptor antagonists reduced re-bleeding and need for surgery

but did not reduce mortality[40]. Subgroup analysis of the data revealed a lower mortality for patients with active bleeding and endoscopic haemostasis who were treated with an 80 mg PPI bolus followed by continuous infusion of 8 mg/h. In contrast, lower doses of PPI reduced re-bleeding but had no effect on mortality. These findings were substantiated by another meta-analysis from the year 2009[45] that found lower re-bleeding rates, need for surgery and mortality in patients with high-dose intravenous PPI therapy. One meta-analysis compared continuous intravenous PPI therapy with bolus intravenous therapy and found bolus therapy as effective as continuous therapy[46]. Lower PPI doses were also associated with less re-bleeding but had no effect on surgery and mortality. Even though there is strong evidence that high-dose PPI therapy combined with endoscopic therapy is highly effective, it is still a subject of intense discussion whether oral PPI therapy is as effective as intravenous therapy. A recent Cochrane analysis was not able to draw a final conclusion since the available studies are not sufficient[47]. A more recent meta-analysis came to the conclusion that oral and intravenous PPI therapies are comparable[48] but also criticized the low quality of the available studies. One recent single-center Asian study that compared high-dose oral PPI therapy with intravenous high-dose PPI therapy in patients with Forrest Ⅰa/Ⅰb or Ⅱa/Ⅱb peptic ulcer found no difference in the risk of re-bleeding between the two groups[49].

Cost effective analyses revealed a clear advantage for high-dose intravenous PPI therapy for three days following successful endoscopic haemostasis[50-52] compared to placebo-as mentioned above, adequate RCTs comparing high-dose intravenous PPI with standard dose intravenous PPI or high dose oral PPI therapy are not yet available.

Two trials showed that PPI therapy in hospitalized patients might be associated with Clostridium difficile infection[53,54]. These findings were substantiated by a recent retrospective cohort study[55]. However, the benefits of PPI treatment in UGIB clearly outweigh this risk.

Post-endoscopic PPI therapy depends on the underlying aetiology of UGIB. In most RCTs, oral PPI therapy was initiated three days after the acute bleeding episode and a dose once daily is thought to be appropriate[56-60]. One trial that investigated the role of PPI therapy in the non-acute setting demonstrated effective ulcer healing with a once daily dose[61]. The duration of therapy is not clearly defined. Patients with Helicobacter negative ulcers who require long-term NSAID therapy might need concomitant continuing PPI therapy.

ENDOSCOPIC MANAGEMENT

Several endoscopic techniques to achieve haemostasis are available. Epinephrine injection is easy to perform and effective in the acute setting but re-bleeding occurs in almost all patients. Therefore, it should be used in combination with another method. The application of clips, thermocoagulation, injection with a sclerosing agent or fibrin or thrombin glue could be performed alone or in combination with epinephrine injection. A new method for the treatment of refractory bleeding is the over the scope clip, that allows the treatment of large defects[62].

First of all, the ulcer bed should be cleaned from blood and blood clots by vigorous irrigation to visualize the underlying lesion. By irrigation alone, the underlying stigmata are exposed in 26% to 43% of cases[63,64]. It is a subject of discussion[45,65] whether adherent clots should be removed by using more vigorous methods like cold guillotining with a snare. There is good evidence that the risk for re-bleeding with clots that remain adherent after washing without endoscopic therapy (only therapy with a proton-pump inhibitor) is as low as 0% to 8%[63,66]. One Asian study that compared endoscopic therapy plus high-dose iv PPI therapy with high-dose iv PPI therapy alone[66] found no re-bleeding in the patients in whom the adherent clots could not be removed by irrigation. Since it is known that the PPI metabolism in Asian people differs from the metabolism in patients with Caucasian background, it is not clear whether these results could be extrapolated to an European or North American population. Furthermore, other studies revealed a re-bleeding risk of 25% to 35%[64,67-69] in high-risk patients. This subject was further evaluated in two meta-analyses: One meta-analysis from 2009[45] comprising 5 RCTs of patients with adherent clots found no advantage of endoscopic *vs* medical therapy alone. These data was substantiated by another meta-analysis comprising 6 RCTs[70] that was also not able to show a reduction in the re-bleeding risk in patients with endoscopic therapy compared to patients with medical therapy alone. On the other hand, a systematic review[71] did not show that endoscopic therapy increased the risk for complications. As a recommendation for clinical practice, patients who are at high risk for re-bleeding and an adherent clot to the ulcer base that is resistant to irrigation, endoscopic therapy after cold guillotining may be beneficial. In patients with a low risk of re-bleeding and those who are Helicobacter positive, high-dose PPI therapy alone might be sufficient.

Numerous studies and meta-analyses studied the efficacy of the available endoscopic techniques in patients with high-risk lesions[45,71-77]. Injection with epinephrine as a monotherapy has been shown to be superior to medical therapy alone but it is clearly inferior to other monotherapies like clip application, thermocoagulation or injection with alcohol, fibrin or thrombin glue[45,71-76,78]. The combination of epinephrine injection with one of the above mentioned therapies for the treatment of high-risk stigmata significantly reduces re-bleeding, need for surgery and mortality[75,78]. The combination of clip application with epinephrine injection is superior to epinephrine injection alone but not to clips alone[72,74]. This is also true for the combination therapy of injection with epinephrine and a second injectate or

thermocoagulation[71]. Complication rates with mono- or combination therapy do not vary significantly[71,79,80].

There is an ongoing discussion whether a routine endoscopic control after the initial endoscopy is necessary or not. The advantages of a programmed second look endoscopy like the identification of residual stigmata that need re-treatment has to be outweighed against potential risks like an increase in ulcer perforation. Five studies[81-85] as well as two meta-analyses of these trials[86,87] investigated the benefit of a second-look endoscopy. The results from these trials were inconclusive due to methodological flaws. A more recent meta-analysis[88] found that routine second-look endoscopy and endoscopic treatment with thermocoagulation as appropriate reduced the risk of re-bleeding. In contrast to the use of a heater probe, second-look endoscopy with injection therapy did not reveal any advantages. Another meta-analysis[89] demonstrated that second look endoscopy decreased re-bleeding and need for surgery but not mortality. The impact of this meta-analysis is decreased by the fact that only one study with concomitant high-dose PPI therapy was included. All of the above mentioned studies had several methodological shortcomings: the included patients were heterogeneous; intervention and control treatments were not standardized. When looking at high risk patients who presented with haemorrhagic shock and/or active bleeding[81] or patients with a very high risk for re-bleeding based on the Forrest criteria[84] second look endoscopy led to a decrease in the re-bleeding rate. A trial, which included a control group that received high-dose iv PPI therapy-as it is standard now-found no benefit for second look therapy[81]. These findings suggest that second look endoscopy is not necessary in patients with high dose PPI therapy. Similar results were obtained from a cost-effectiveness study[90] that compared second-look endoscopy in selected high-risk patients only to second-look endoscopy in all patients and found endoscopy in selected patients to be more effective and less expensive. From the available data, routine second-look endoscopy is not recommended. However, patients at high-risk of re-bleeding might benefit from a programmed second-look endoscopy.

The highest risk for re-bleeding in patients treated with a combination of endoscopic and PPI therapy is within the first 72 h after the initial bleeding episode. Sixty to 76% of re-bleeding occurred in the first three days[56,57,59]. Thus, patients with bleeding from high-risk lesions should be treated as in-patients for at least three days. Patients at high-risk for re-bleeding should be monitored more intensely on an intensive or intermediate care unit for at least 24 h. Nevertheless, selected patients with ulcers not more than 15 mm in size, no relevant co-morbidity, appropriate family support and absence of haemorrhagic shock at presentation could be safely managed as outpatients[91].

If haemostasis could not be achieved or repeated re-bleeding occurs, it is associated with a high mortality. Patients rarely die because of exsanguination but because of problems that arouse from associated co-morbidity like cardiac events, acute kidney failure, infection or stroke. Accordingly, patients in whom endoscopic therapy failed should be admitted to surgery without delay. In patients who are high-risk candidates for surgery, percutaneous or transcatheter arterial embolization might be an alternative[92-99]. Data from uncontrolled trials revealed technically success rates from 52% to 98% with a reported re-bleeding rate of 10% to 20%[92-99]. The reported periprocedural mortality is as high as 25% to 30%. This is most likely due to the negative selection of patients with advanced age and co-morbidity to unstable to undergo surgery[92,93,95,97]. Possible complications of the procedure are mainly bowel ischemia or infarction of the stomach, liver or spleen[94,95,98-101].

Helicobacter pylori

Patients with UGIB from ulcers or haemorrhagic gastritis should be tested for *Helicobacter pylori* (*H. pylori*) infection and should undergo eradication therapy if *H. pylori* is present. The effectiveness in prevention of re-bleeding in peptic ulcer disease was demonstrated in a meta-analysis[102]. It is well known that *H. pylori* testing might reveal false negative results in the setting of an acute bleeding episode[103]. The reason is not fully understood but is most likely due to the alkaline setting that results in pH buffering from blood in the stomach[103] as well as from PPI therapy, which is dose-dependent. Therefore, an initially negative testing for *H. pylori* should be repeated during follow-up.

NSAID AND ASA USE

The use of NSAID and ASA is associated with a markedly increased risk of ulcer disease. Several studies addressed this issue and investigated whether the combination of NSAID and PPI decreased the risk for recurrent bleeding and also compared traditional NSAID with cyclooxygenase-2 (COX-2) inhibitors. Two small trials with a relatively low patient number showed that the combination of NSAID with PPI therapy as well as COX-2 inhibitor therapy alone lowered the risk for recurrent bleeding compared to historical controls on a therapy with NSAID alone[104-106]. These findings are substantiated by population-based studies that also found a reduction in UGIB by adding PPI to traditional NSAID or by therapy with a COX-2 inhibitor alone[3,107]. The combination of a COX-2 inhibitor with PPI further decreased the bleeding risk compared to a COX-2 inhibitor alone[108]. These finding were in-line with the results of a meta-analysis of three RCTs[109] and two studies[108,110] that also revealed a lower bleeding risk in patients who were on a combination of COX-2 inhibitors and PPI compared to patients on a COX-2 inhibitor alone.

Although COX-2 inhibitors, especially in combination with PPI therapy, lower the risk for UGIB, it was

demonstrated that the use of a COX-2 inhibitor is associated with an increased risk of cardiovascular events[111,112].

In clinical practice, NSAID therapy should be discontinued if possible. In patients without an increased risk for cardiovascular events and the need for NSAID therapy, patients should receive the combination of a COX-2 inhibitor and PPI. However, possible long-term side effects of PPI therapy should be kept in mind.

Things are more complicated in patients who receive cardioprotective ASA therapy. Prolonged discontinuation of ASA therapy (*e.g.,* to complete ulcer healing) is associated with an increase in adverse cardiovascular events[113,114]. In most cases, thrombotic events occur between 7 and 10 d after discontinuation of ASA therapy[113,115,116]. This is well explained by the fact that ASA therapy inhibits irreversibly platelet function and the half-life of platelets of around 7 d. In patients at high risk of cardiovascular events, the early reintroduction of ASA therapy outweighs the risk of re-bleeding[117]. Discontinuation of ASA therapy in patients with acute ulcer bleeding was shown to increase the eight-week mortality rate, whereas the early reintroduction of ASA therapy in combination with PPI revealed an insignificant trend to a higher re-bleeding rate only. The findings of another RCT[117] were even more convincing with no reported re-bleeding in patients on ASA therapy and ulcer bleeding in whom therapy with ASA or clopidogrel in combination with PPI was initiated one day after endoscopy. In summary, therapy with ASA or clopidogrel in patients with cardiovascular risk factors should be restarted as soon as the risk for cardiovascular events outweighs the risk for re-bleeding.

Compared to ASA, the risk of ulcer bleeding associated with clopidogrel mono therapy is lower, but is still as high as 14%[118,119]. Clopidogrel therapy alone has a higher re-bleeding risk than ASA therapy combined with PPI therapy[118,119]. Clopidogrel requires cytochrome P450 isoenzyme CYP2C19 to be converted to its active metabolite[120]. Since PPI and clopidogrel compete for the same cytochrome P450 isoenzyme, PPI may decrease the effect of clopidogrel. An increase in cardiovascular events in patients who received clopidogrel and PPI therapy in combination has been shown by some observational studies[121-125], but other studies did not reveal an increase in cardiovascular events[125,126]. Since reliable RCT addressing this issue are lacking, the interval between the intake of PPI and clopidogrel should be as long as possible (*e.g.,* PPI in the morning and clopidogrel in the evening).

CONCLUSION

Non-variceal UGIB could be a life-threatening event, especially in older patients with co-morbidities. With a combination of endoscopic and PPI therapy haemostasis could be achieved in the majority of patients. When endoscopic measures fail, patients should undergo surgery or interventional radiology without delay. In peptic ulcer disease, testing for *H. pylori* is mandatory and eradication reduces the re-bleeding risk. Caution is necessary in patients that need a long-term therapy with NSAID. In patients at risk, NSAID have to be combined with PPI therapy.

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