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TOPIC HIGHLIGHT

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Management of acute nonvariceal upper gastrointestinal bleeding: Current policies and future perspectives

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Abstract

Acute upper gastrointestinal bleeding (UGIB) is a gastroenterological emergency with a mortality of 6%-13%. The vast majority of these bleeds are due to peptic ulcers. Nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* are the main risk factors for peptic ulcer disease. Endoscopy has become the mainstay for diagnosis and treatment of acute UGIB, and is recommended within 24 h of presentation. Proton pump inhibitor (PPI) administration before endoscopy can downstage the bleeding lesion and reduce the need for endoscopic therapy, but has no effect on rebleeding, mortality and need for surgery. Endoscopic therapy should be undertaken for ulcers with high-risk stigmata, to reduce the risk of rebleeding. This can be done with a variety of modalities. High-dose PPI administration after endoscopy can prevent rebleeding and reduce the need for further intervention and mortality, particularly in patients with high-risk stigmata.

INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is the most common gastroenterological emergency and has a considerable morbidity and mortality. Management strategies have changed dramatically over recent decades due to the introduction of acid suppressive therapy [histamine-2 receptor antagonists and especially proton pump inhibitors (PPIs)] and endoscopic therapy. This review deals with the current standards and future perspectives in management of acute nonvariceal UGIB.

EPIDEMIOLOGY

The incidence rates of UGIB demonstrate a large geographic variation ranging from 48 to 160 cases per 100 000 population, with consistent reports of higher incidences among men and elderly people[1-5]. Possible

Table 1 Mortality rates in patients with upper gastrointestinal bleeding in various studies

	Czernichow *et al*[5]	Paspatis *et al*[4]	Van Leerdam *et al*[3]	Di Fiore *et al*[7]	Theocharis *et al*[1]	Hearnshaw *et al*[10]
Country	France	Greece	The Netherlands	France	Greece	United Kingdom
Year of publication	2000	2000	2003	2005	2008	2010
No. of patients	2133	353	769	453	353	6750
Mortality rate total (%)	14.3	5.6	13	7.2	6.5	7.4
Varices (%)	22.8	21.4	16	15.2	9	15
Peptic ulcer (%)	13.3	2.6	14	5	4.2	8.7

Table 2 Causes of upper gastrointestinal bleeding according to recent epidemiological studies[1,3-5,7,10]

	%
Peptic ulcer	31-67
Erosive	7-31
Variceal bleeding	4-20
Oesophagitis	3-12
Mallory-Weis	4-8
Neoplasm	2-8
Other	2-8
None	3-19

explanations for the reported geographic variation in incidence are differences in definition of UGIB in various studies, population characteristics, prevalence of ulcerogenic medication, in particular aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and *Helicobacter pylori* (*H. pylori*) prevalence. Some but not all time-trend studies have reported a significant decline in incidence of acute UGIB, especially peptic ulcer bleeding, in recent years[1,3,6]. This decline is likely due to a combination of factors, including decreasing prevalence of gastric colonization with *H. pylori*[1], the use of eradication therapy in patients with ulcer disease, and the increased use of PPI therapy, both in general and in patients using aspirin and NSAIDs in particular.

Despite the introduction of therapeutic endoscopy and acid-suppressive therapy, the overall mortality of UGIB has remained stable over recent decades and is still 6%-14% in most studies (Table 1)[1,3-5,7]. The majority of deaths do not directly result from exsanguination, but are related to poorly tolerated blood loss and resultant shock, aspiration, and therapeutic procedures. As such, mortality from UGIB is strongly associated with advanced age and presence of severe comorbidity. The risk of mortality increases with rebleeding, which is thus another major outcome parameter[5]. The incidence of rebleeding in patients with UGIB shows a wide range from 5% to more than 20%, depending on several factors[3,4]. These firstly include the etiology of the bleeding, with rebleeding being more common in patients with variceal bleeding (25%) and uncommon in patients with small mucosal lesions such as Mallory-Weiss lesions. A second factor that determines the frequency of rebleeding is the timing and use of adequate endoscopic therapy. There is strong evidence that the risk of rebleeding is highest in the initial period of admission, and a 24-h time frame for endoscopic therapy is internationally recommended as the optimal window of opportunity[8,9]. Mortality amongst those with recurrent bleeding is considerably higher, therefore, rebleeding must be prevented whenever possible[8].

Peptic ulcer bleeding (PUB) is the most common cause of UGIB, accounting for 31%-67% of all cases, followed by erosive disease, variceal bleeding, esophagitis, malignancies and Mallory-Weis tears (Table 2)[1,3-5,7,10]. In 2%-8% of cases, uncommon causes such as Dieulafoy's lesion, hemobilia, angiodysplasia, vasoenteric fistula, and gastric antral vascular ectasia have been found. In the remainder of this paper, we mainly focus on PUB, yet the approach to and treatment of any patient with nonvariceal UGIB is for the most part comparable. Possible differences will be discussed in the section on endoscopic therapy.

In the subgroup of patients with PUB, bleeding from duodenal ulcers is slightly more frequent than from gastric ulcers[1,4]. NSAID use and *H. pylori* infection are independent risk factors for UGIB, especially PUB[8,11]. The prevalence of *H. pylori* infection in PUB patients varies between 43 and 56%[12-14], and treatment of *H. pylori* significantly reduces the rebleeding rate according to some randomized controlled trials[15,16].

PRE-ENDOSCOPIC MANAGEMENT

Initial resuscitation and risk stratification

Patients with UGIB can present with various symptoms such as hematemesis, hematochezia, melena, or progressive anemia. Immediate evaluation and appropriate resuscitation is of major importance in these patients. Stratification of patients in low- and high-risk categories for rebleeding and mortality can be done using the Blatchford and initial Rockall scores (before endoscopy), or complete Rockall score (after endoscopy) (Table 3)[17,18]. The Blatchford score is more focused on clinical symptoms and laboratory results, whereas the Rockall score considers age as a parameter.

Resuscitation includes intravenous administration of fluids, and supplemental oxygen, correction of severe coagulopathy, and blood transfusion when needed. The threshold for blood transfusion depends on the underlying condition, rate of bleeding, and vital signs of the patient, but is generally set at a hemoglobin level of $\leqslant$ 70 g/L[19]. A recent meta-analysis regarding outcomes following red blood cell transfusion in patients with UGIB, however, suggests that red blood cell transfusion is associated with

Table 3 Comparison of Blatchford and Rockall risk scoring systems

Risk factor	Blatchford score		Initial Rockall score	
	Parameter	Score	Parameter	Score
Age (yr)	-		60-79	1
			⩾ 80	2
Systolic blood pressure (SBP) (mmHg)	100-109	1	< 100	2
	90-99	2		
	< 90	3		
Heart rate (bpm)	> 100	1	> 100 with SBP ⩾ 100	1
Clinical presentation	Melena	1	-	
	Syncope	2		
Comorbidity	Hepatic disease	2	CHF, IHD, major comorbidity	2
	Cardiac failure	2	Renal or liver failure, or disseminated cancer	3
Blood urea, mg/dL (mmol/L)	18.2-22.3 (6.5-7.9)	2	-	
	22.4-27.9 (8-9.9)	3		
	28-69.9 (10-24.9)	4		
	⩾ 70 (⩾ 25)	6		
Hemoglobin, g/dL (mmol/L)	F: 10-11.9 (6.2-7.4)	1	-	
	M: 12-12.9 (7.5-8)			
	M: 10-11.9 (6.2-7.4)	3		
	F/M: < 10 (< 6.2)	6		
			Complete Rockall score	
Endoscopic diagnosis	-		Non-malignant, non-Mallory-Weis diagnosis	1
			Upper GI tract malignancy	2
Evidence of bleeding	-		Blood, adherent clot, active bleeding	2

M: Male; F: Female; CHF: **Congestive heart failure; IHD: Ischemic heart** disease.

higher mortality and rebleeding rate. The conclusions of this study were limited by the small size of the studies and the large volume of missing data. In addition, the possibility that patients who present with more severe and active bleeding are more rapidly transfused, acted as a potential major confounder in these analyses[20]. This means that prospective studies need to be done with strict predetermined transfusion protocols, and that for now, the risks and benefits of blood transfusion must be carefully weighed individually.

Pre-endoscopic pharmacotherapy

Administration of PPIs before endoscopy has become common practice in patients suspected with PUB. A strongly acidic environment leads to inhibition of platelet aggregation and plasma coagulation as well as to lysis of already formed clots[21]. PPIs quickly neutralize intraluminal gastric acid, which results in stabilization of blood clots. In the longer term, antisecretory therapy also promotes mucosal healing. A recent systematic review has shown that pre-endoscopic PPI administration significantly reduces high-risk stigmata at index endoscopy (37% *vs* 46% respectively, OR: 0.67; 95% CI: 0.54-0.84) and need for endoscopic therapy (9% *vs* 12% respectively, OR: 0.68; 95% CI: 0.50-0.93). However, no effect on clinically important outcome measures such as rebleeding, mortality and need for surgery was seen[22].

Another pharmacotherapeutic approach includes the use of prokinetics before endoscopy, in particular, erythromycin or metoclopramide. A meta-analysis of five studies assessing a total of 316 patients with acute UGIB has found a significant reduction in the need for repeated endoscopy (OR: 0.55; 95% CI: 0.32-0.94) in the prokinetic treatment group compared to the reference group (placebo or no treatment). The groups did not differ in the need for blood products, hospital stay, and need for surgery[23]. Therefore, prokinetics are not routinely recommended, but can be useful in patients who are suspected of having substantial amounts of blood in the stomach[9]. Administration of PPIs and prokinetics should however not delay endoscopy.

ENDOSCOPY

Time to endoscopy

Endoscopy has become a valuable and indispensable tool for diagnosis and treatment of UGIB[24,25]. It allows for identification of the bleeding source and application of treatment in the same session. The optimal timing for endoscopy remains under debate. Emergency endoscopy allows for early hemostasis, but can potentially result in aspiration of blood and oxygen desaturation in insufficiently stabilized patients. In addition, extensive amounts of blood and clots in the stomach can hinder targeted treatment of the bleeding focus, which results in repeated endoscopic procedures. International consensus guidelines recommend early endoscopy within 24 h of presentation, because it significantly reduces the length of hospital stay and improves outcome[19]. Very early endoscopy (< 12 h) has so far not been shown to provide additional benefit in terms of reduction of rebleeding, surgery and mortality, compared with later endoscopy (within 24 h)[26-29]. However, emergency endoscopy should be considered in patients with severe bleeding.

Endoscopic therapy for PUB

The aim of therapeutic endoscopy is to stop any ongoing bleeding and prevent rebleeding. Several techniques, including injection therapy, ablative therapy and mechanical therapy have been studied over recent decades[24,30,31]. Depending on the appearance of the bleeding focus and the related risk for persistent or recurrent bleeding, a suitable technique should be chosen. In PUB, patients with active bleeding ulcers or a nonbleeding visible vessel in an ulcer bed are at highest risk of rebleeding and therefore need prompt endoscopic hemostatic therapy (Figures 1 and 2)[32]. Patients with low-risk stigmata (a clean-based ulcer or a pigmented spot in an ulcer bed) do not require endoscopic therapy.

The role of endoscopic therapy for ulcers with adherent clots has been a topic of debate[19]. The risk of rebleeding depends on underlying lesions, so that clot re-

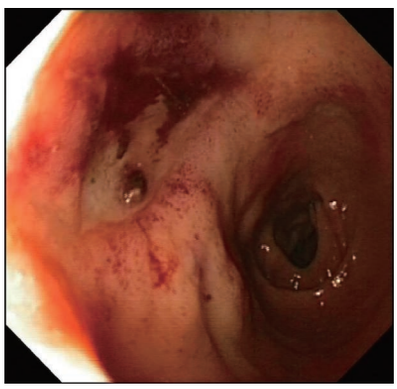

Figure 1 Ulcer with visible vessel.

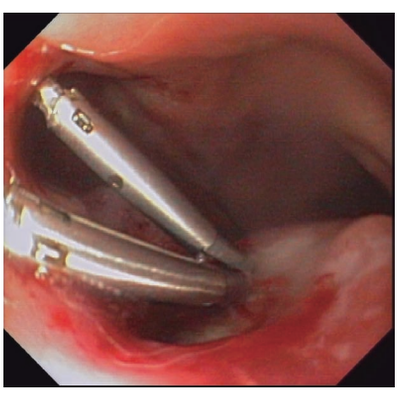

Figure 2 Ulcer with visible vessel after hemoclip placement.

moval should be attempted by vigorous irrigation. Stigmata revealed after clot removal are of high risk in about 70% of cases[33]. In a meta-analysis including 240 patients from six different studies, comparing endoscopic *vs* medical therapy for peptic ulcers with adherent clots, rebleeding was significantly lower in the endoscopic therapy group compared with the control group (8% *vs* 25%, $P = 0.01$)[34]. Another meta-analysis, however, has shown no benefit of endoscopic therapy for bleeding peptic ulcers with adherent clots[35]. These discrepancies could be attributed to inclusion of different studies and heterogeneity in statistical analysis. At present, endoscopic therapy should be considered, although intensive PPI therapy alone might be sufficient in ulcers with adherent clots[19].

Epinephrine injection therapy promotes initial hemostasis by a combination of vasospasm and local tamponade. This effect declines after 20 min, and requires additional treatment with a more durable technique. In several meta-analyses, no superiority of one specific technique was proven; in particular, hemoclip placement, thermocoagulation (e.g., heater probe), and electrocoagulation (e.g., Gold probe, BICAP probe) all seem equivalent alternatives[24,30,31,36]. Patients with recurrent bleeding can usually be managed by endoscopic therapy. However, emergency surgery or angiographic embolization is required on occasion. There have been no randomized trials that have compared surgery and angiographic embolization.

A new promising endoscopic application is the use of a chemical compound which, when sprayed as nanopowder on active bleeding, can lead to immediate hemostasis, with coverage of the bleeding ulcer with a powder layer. In a pilot study of 15 patients with active ulcer bleeding treated with this nanopowder, immediate hemostasis was achieved in 93%, and one patient had recurrent bleeding. No adverse events were reported during the 30-d follow-up[37]. Further studies with this product are ongoing and will elucidate if application is also beneficial for other causes of nonvariceal UGIB.

Endoscopic therapy for other causes of nonvariceal UGIB

Treatment and prevention of (bleeding from) erosions depends upon the cause (e.g., drug-induced, mechanical, or inflammatory). Most cases respond well to PPIs. The offending agent should be discontinued whenever possible and, if present, *H. pylori* should be eradicated. Acute bleeding sometimes needs endoscopic therapy, similar to that for PUB[38].

Hemorrhage due to neoplastic lesions is often difficult to manage because of the diffuse character of the bleeding and vulnerability of the mucosa. Primary endoscopic therapy is recommended, but additional surgical consultation is sometimes necessary. In cases with diffuse tumor bleeding in a palliative setting, radiotherapy is often the treatment of choice.

Most bleeding from Mallory-Weiss tears stops spontaneously. Patients with stigmata of active bleeding, however, might require interventional endoscopy[39]. Endoscopic therapy is the first choice in bleeding Dieulafoy's lesions and is usually performed with clipping or banding of the lesion[40].

The current standard for endoscopic treatment of bleeding angiodysplasia consists of coagulation therapy. Sometimes, pharmacological agents such as estrogen and progesterone, octreotide or thalidomide are given, but their effects remain controversial.

Gastric antral vascular ectasia responds best to endoscopic ablation of the lesion.

POSTENDOSCOPIC MANAGEMENT

Antisecretory therapy

Pharmacotherapy plays a second major role in the treatment of UGIB. PPI therapy is superior over histamine-2 receptor antagonists[19]. PPIs can be administered orally or intravenously depending on the rebleeding risk. In a randomized placebo-controlled trial of 767 multiethnic PUB patients treated with endoscopic therapy because of high-risk stigmata, high-dose intravenous PPI (80 mg esomeprazole bolus, 8 mg/h continuous infusion for 72 h) significantly reduced rebleeding (5.9% *vs* 10.3%, $P = 0.03$) and the need for endoscopic retreatment[41]. Similar results were found by meta-analysis; high-dose intravenous PPI after endoscopic therapy significantly reduced rebleeding [relative risk (RR): 0.40; 95% CI: 0.28-0.59], need for sur-

gery (RR: 0.43; 95% CI: 0.24-0.58) and mortality (RR: 0.41; 95% CI: 0.20-0.84) compared with placebo/no therapy[35]. These data support the guideline recommendation to give high-dose continuous intravenous PPI therapy to patients with PUB with high-risk stigmata.

Additionally, all patients with PUB should be discharged with a prescription for a single-daily-dose oral PPI to reduce the risk of recurrent bleeding. The duration and dose of the PPI depend on the underlying etiology and additional medication use[19].

H. pylori eradication therapy

Testing for *H. pylori* is recommended in all patients with PUB[19]. This should be followed by eradication therapy for those who are *H. pylori*-positive, with subsequent assessment of the effect of this therapy, and renewed treatment in those in whom eradication fails. The efficacy of eradication therapy and maintenance antisecretory therapy for the prevention of rebleeding has been assessed in a meta-analysis of randomized trials. This revealed a significantly lower risk of rebleeding in the *H. pylori* eradication group, that is, 1.6% *vs* 5.6% within a median follow-up of 12 mo. When only patients with successful *H. pylori* eradication were included, the rebleeding rate was even lower (1%)[42]. Therefore, confirmation of eradication is recommended. Diagnostics tests for *H. pylori* have a low negative predictive value in the setting of acute UGIB. This might be due to technical difficulties to collect a sufficient number of representative biopsies, or inaccuracy of the test in a more alkaline environment caused by the blood[43]. Initial negative results on biopsies obtained in the acute setting must therefore be interpreted with caution and repetition of the test during follow-up is recommended[19].

CONCLUSION

The management of UGIB has changed dramatically over recent decades. Endoscopic therapy and pharmacotherapy have become the mainstay in management. Early endoscopy within 24 h of presentation, or earlier in selected cases with signs of ongoing bleeding, improves outcome and reduces length of hospital stay. Endoscopic epinephrine injection in combination with another endoscopic technique reduces the risk for rebleeding and related mortality in patients with high-risk ulcers. Adequate *H. pylori* eradication and PPI therapy after discharge can bring the rebleeding and mortality rates further down.

Ongoing development is expected especially in the area of development of transfusion policies, and new tools for endoscopic hemostasis. Further studies are needed to clarify the optimal approach for patients with adherent clots. These developments should help to reduce the persistent high mortality rate of UGIB, a disease which nowadays in particular occurs in elderly patients with comorbidity and medication use.

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