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Сучасне фармакологічне лікування у випадку кровотечі з верхнього відділу травної системи

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Кровотеча з верхніх відділів шлунково-кишкового тракту – поширена причина госпіталізації. Наріжним каменем роботи з високоризикованими ураженнями (сильна кровотеча чи відсутність кровотечі з помітними судинами) є належна реанімація з подальшою ендоскопічною оцінкою. Фармакологічна терапія використовується на всіх етапах лікування у випадку варикозної та неварикозної кровотечі. Інгібітор протонної помпи та прокінетики можна вводити до ендоскопії разом із вазоактивними препаратами й антибіотиками, що застосовуються в разі підозри на варикозну кровотечу. Як тимчасовий засіб можна використовувати епінефрин, щоб покращити візуалізацію під час ендоскопії, але не варто застосовувати самостійно. Місцева ендоскопічна терапія виявилася перспективною в досягненні гемостазу. Після ендоскопії пацієнтам, які потребують ендотерапії і вазоактивних препаратів, потрібно призначити високі дози інгібітора протонної помпи й продовжувати лікування антибіотиками в разі підтвердженої варикозної

кровотечі. Час відновлення прийому протитромбозних препаратів залежить від препарату, що використовується, і ризику тромбозу.

Ключові слова: кровотеча з верхніх відділів шлунково-кишкового тракту, крововиливи з верхніх відділів шлунково-кишкового тракту, варикозна кровотеча, неварикозна кровотечі, лікування кровотечі з верхніх відділів шлунково-кишкового тракту.

Current Pharmacological Management in Upper Gastrointestinal Bleeding

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Upper gastrointestinal bleeding is a common reason for presentation to the hospital. Appropriate resuscitation followed by endoscopic assessment and endotherapy for high-risk lesions (active bleeding or non-bleeding with visible vessels) forms the cornerstone of management. Pharmacological therapies are utilised at each stage of management in both variceal and non-variceal bleeding. Proton pump inhibitors and prokinetic agents can be administered pre-endoscopically with vasoactive medication and antibiotics utilised in suspected variceal bleeding. Epinephrine may be used as a temporising measure to improve visualisation during endoscopy but should not applied as a single agent. Topical endoscopic therapies have also shown promise in achieving haemostasis. Following endoscopy, a high dose of proton pump inhibitor should be given to patients who require endotherapy and vasoactive medications, and antibiotics continued in confirmed variceal bleeds. The timing of resumption of antithrombotic medication is dependent on the agent utilised and underlying thrombotic risk.

Keywords: Upper Gastrointestinal Bleeding, Upper Gastrointestinal Haemorrhage, Variceal Bleeding, Non-Variceal Bleeding, Pharmacological Management of Upper Gastrointestinal Bleeding.

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Introduction

Upper gastrointestinal bleeding (UGIB) is a common cause of acute hospitalisation, with an incidence of 67–172 cases per 100,000 population (1,2). Concomitant with the development of endo-therapeutic techniques, pharmacological interventions have evolved with the use in both non-variceal and variceal bleeding. Despite the advent of effective *Helicobacter pylori* (*H. pylori*) eradication therapy and proton pump inhibitor, peptic ulcer disease remains the most common cause of UGIB. (3) Aging populations with more significant comorbidities are associated with poor outcomes (4) and have increased complexity of management. Increased utilisation of antiplatelet and anticoagulant medications has also complicated the management of UGIB, with careful balance required between the risk of bleeding and thrombosis. This article will review the current pharmacological approaches to UGIB in the pre-endoscopic, endoscopic assessment and post-endoscopic stages.

Sources and selection criteria

Between July 2023 and September 2023, a review of PubMed, Embase and Ovid Medline was performed with no date restriction. Relevant terms were searched, including 'upper gastrointestinal bleeding', 'non-variceal bleeding management' and 'variceal bleeding management'. Preference was given to peer-reviewed meta-analyses, systematic reviews, and well-constructed randomised control trials. Multiple comprehensive international guidelines exist for both non-variceal and variceal UGIB. These are referenced throughout the article and highlighted where differences exist.

Pre-endoscopic pharmacological management

Where appropriate, high-quality resuscitation and replacement of blood product remains the cornerstone in improving the outcome of UGIB. Pre-endoscopically, several agents can be utilised which have been shown to improve outcomes or aid endoscopic intervention (see Table 1 for summary of current pharmacological interventions).

Proton pump inhibitors (PPI)

A Cochrane meta-analysis of six randomised controlled studies (RCT) including 2223 patients showed a significant reduction in pa-

tients with stigmata of haemorrhage (defined as active spurting, bleeding or non-bleeding visible vessel and adherent clot) at index endoscopy with pre-endoscopic PPI therapy (OR 0.68, 95% CI 0.50 to 0.93) but no significant decrease in mortality (OR 1.12, 95% CI 0.72–1.73), need for surgery (OR 0.96, 95% CI 0.68–1.35) or rebleeding (OR 0.81, 95% CI 0.61–0.91). (5) Despite this, the use of pre-endoscopic PPI remains prevalent. The 2015 UK National Confidential Enquiry into Patient Outcome and Death reported that in 73% of cases (150/206), acid suppression therapy was commenced prior to definitive diagnosis (6). This discrepancy may be due to clinicians' desire to start a practical intervention pre-endoscopically. Pre-endoscopic PPI may reduce the need for costly endo-therapeutic intervention, but this saving must be offset by the blanket use of PPI if pursuing this.

Recent European non-variceal UGIB guidelines suggest pre-endoscopic high-dose PPI may be considered in patients presenting with UGIB to downstage endoscopic stigmata but should not delay endoscopy (7). Authors of the American guidelines were unable to reach a recommendation for or against pre-endoscopic PPI (8).

Prokinetic therapies

Significant extravasation of blood and resulting clot formation in the GI tract during UGIB can impede the identification of bleeding points and the application of endotherapy. Prokinetic agents may allow improved interrogation of gastric mucosa, risk stratification of lesions and therapy by enhancing gastric emptying.

A meta-analysis of eight RCTs, including 598 patients, reported erythromycin administration pre-endoscopy significantly improved adequate gastric mucosa visualisation (OR 4.14, 95% CI 2.01–8.53, $p < 0.01$) with a number needed to treat to optimise visualisation 4. Need for second look endoscopy and length of hospital stay were also significantly reduced (OR 0.51, 95% CI 0.34–0.77, $p < 0.01$ and mean days -1.75, 95% CI -2.43- -1.06, $p < 0.01$ respectively). No difference was observed in the requirement for transfusion, need for surgery or duration of procedure (9). A subsequent RCT involving 43 patients showed that satisfactory visualisation was

achieved in 92.8% of patients given erythromycin pre-endoscopically vs 60.0% of patients given gastric lavage. However, this finding did not reach significance (10).

American guidelines suggest intravenous administration of 250mg erythromycin (most commonly prescribed in studies) over 30–120 minutes pre-endoscopically can be considered, with European guidance suggesting its use in selected patients (7,8).

Tranexamic acid (TXA)

A synthetic lysine derivative, TXA (trade name Cyclokapron), reversibly blocks the lysine binding site on plasminogen, exerting an antifibrinolytic effect (11). It is widely utilised in

the management of major bleeding in obstetrics (12) surgery and traumatic haemorrhage, where the CRASH-2 RCT showed a reduction in mortality of one-third when TXA was given within 3 hours (13). Within the context of UGIB, several relatively small studies reported differing outcomes with the use of TXA (14,15), and a Cochrane meta-analysis performed in 2014 concluded that TXA use appeared to have a beneficial effect on mortality, but more research was required. (16) Subsequent to this, the HALT-IT trial, an international RCT involving 12009 patients showed no difference in death due to bleeding within five days in TXA vs placebo groups (RR 0.99, 95%CI 0.82–1.18) and an increase in venous thromboembolic events (pulmonary embolism and deep vein throm-

Table 1.

Summary of current pharmacological interventions for UGIB

	Beneficial pharmacological interventions	Non-beneficial pharmacological interventions
Pre-endoscopic	<p>Prokinetic therapies 250mg erythromycin over 30-120 minutes Improved visualisation of gastric mucosa For use in selected patients</p>	<p>Tranexamic acid (Cyclokapron) No improvement in mortality described with increased risk of VTE event</p>
	<p>Proton pump inhibitor Reduction in stigmata of bleeding at index endoscopy but no significant difference seen in mortality, need for surgery or rebleeding Utilised in some centres pre endoscopically</p>	
	<p>Suspected Variceal Bleeding Vasoactive medication Vasopressin and analogues or Somatostatin and analogues Reduction in failure to control bleeding and reduced mortality</p> <p>Broad spectrum antibiotics Choice dependant on local sensitivities Reduction in mortality, bacterial infection and rebleeding</p>	
Endoscopic	<p>Topical haemostatic powders Currently considered temporising measure considered in patients with persistent bleeding refractory to standard modalities.</p>	<p>Epinephrine injection as monotherapy Should be utilised as temporising measure for improved visualisation enabling secondary haemostatic modality</p>
Post-endoscopic	<p>Proton pump inhibitor Reduction in rebleeding and mortality with usage post endoscopically. Often administered as 72hr infusion recent literature suggests IV bolus or high dose oral PPI may be considered.</p> <p>Helicobacter pylori eradication Should be administered if appropriate. Delayed eradication therapy increases risk of recurrent bleeding</p> <p>Confirmed Variceal Bleeding Vasoactive medication Continue for 2-5 days Broad spectrum antibiotics Continue for 5-7 days Carvedilol Evolving evidence of improved haemodynamic and clinical outcomes with long term use. Research ongoing</p>	

bosis) in the TXA group (48/5952 (0.8%) vs 26/5877 (0.4%), RR 1.85, 95%CI 1.15–2.98) (17). TXA use is therefore not recommended by any guideline outside of clinical trials.

Pre-endoscopic pharmacological management of suspected variceal bleeding

Antibiotic therapy

Mortality from variceal bleeding is associated with Child's Pugh (CP) score, renal dysfunction and bacterial infection (18). While the aetiology of bleeding is not confirmed until endoscopy if variceal bleeding is suspected, current guidelines advocate the early use of prophylactic antibiotics for up to seven days (19,20), with intravenous third-generation cephalosporins appearing more effective in UGIB than oral norfloxacin (21). A systematic review of 12 RCTs, including 1241 patients, showed that antibiotic prophylaxis was associated with reduced mortality (RR 0.79, 95% CI 0.63–0.98), bacterial infections (RR 0.35, 95% CI 0.26–0.47) and rebleeding (RR 0.53, 95% CI 0.38–0.74) (22).

Despite prophylactic antibiotic therapy use in variceal bleeding, bacterial infection remains problematic. A recent post hoc analysis performed on an international database designed to examine the role of pre-emptive transjugular intrahepatic portosystemic shunts in patients with cirrhosis and variceal bleeding reported that 19% (323/1656) of patients who received prophylactic antibiotics developed a bacterial infection during their admission. Respiratory infection accounted for 43.6% and was independently associated with advanced liver failure (CP-C) (OR 3.1; 95% CI 1.4–6.7), grade III–IV encephalopathy (OR 2.8; 95% CI 1.8–4.4) and intubation for endoscopy (OR 2.6; 95% CI 1.8–3.8) (23).

Vasoactive medication

Two classes of vasoactive medications, vasopressin and analogues and somatostatin and analogues, have been shown to significantly reduce 7-day mortality and improve haemostasis in acute variceal bleeding (24).

Vasopressin is a potent splanchnic vasoconstrictor that reduces portal pressure. Compared to no treatment, a pooled analysis of 4 RCTs showed vasopressin reduced failure to

control variceal bleeding (OR 0.22, 95% CI 0.12–0.43), though this finding did not translate to a survival advantage (25). Despite the concomitant use of nitro-glycerine to lessen harmful effects, (26) concerns regarding vasopressin's unfavourable side effects, including reduced coronary flow and decreased cardiac output, have limited its use.

Terlipressin, an analogue of vasopressin, acts through immediate systemic vasoconstriction and subsequent portal haemodynamic effects through slow conversion to vasopressin (20). This more extended biological activity is associated with fewer side effects, including cardiac and peripheral ischaemia (27). A meta-analysis of seven RCTs, including 443, showed Terlipressin reduced failure to control bleeding and improved survival (RR 0.66, 95% CI 0.55–0.93 and RR 0.55 95% CI 0.49–0.88 respectively) (28).

Somatostatin and its analogue, octreotide, reduce portal pressure through selective splanchnic constriction. Both somatostatin and octreotide are administered via continuous infusion. In a double-blind, prospective trial in patients with variceal bleeding treated with sclerotherapy, somatostatin was shown to significantly decrease bleeding at endoscopy and the quantity of packed red cells required over 120 hours (2.64 units, SD 0.35 in the somatostatin group vs 3.62 units SD 3.62 in the placebo group $p=0.05$) (29).

A meta-analysis comparing the efficacy of Terlipressin, somatostatin and octreotide in variceal bleeding reported the use of vasoactive agents was associated with a significantly lower risk of 7-day mortality (RR 0.74, 95% CI 0.57–0.95, $p=0.02$) and improvement in haemostasis (RR 1.21, 95% CI 1.13–1.30, $p<0.001$) but no difference in efficacy was seen between the agents. (24) A subsequent large multicentre RCT involving 780 patients also showed no significant difference in the efficacy of Terlipressin, somatostatin and octreotide with 5-day treatment success, defined as control of bleeding without rescue treatment 86.2%, 83.4%, and 83.8% respectively ($p=0.636$). Similar mortality and active bleeding at primary endoscopy rates were also observed (30).

All major variceal bleeding guidelines suggest the commencement of a vasopressor at

admission and continuation for 2–5 days unless there are contraindications to their use (19,20,31,32). There is currently no data on the use of vasoactive medication in variceal bleeding secondary to non-cirrhotic portal hypertension.

Antithrombotic agents

The concomitant use of antiplatelet and anticoagulant agents for the management of cardiovascular and cerebrovascular disease in patients presenting with UGIB can present a major clinical challenge. The majority of deaths after UGIB are due to non-bleeding causes, often related to cardiovascular comorbidity. Therefore, a careful balance between bleeding and thrombotic risk is required (33,34).

Antiplatelets

The decision to continue aspirin monotherapy in UGIB can be stratified by whether the indication is primary or secondary cardiovascular prevention. A meta-analysis of six primary prevention trials including 95000 patients reported an absolute annual risk reduction of 0.07% of adverse severe vascular events with a number requiring treatment equal to 1,429 (35,36). The risk of a major cardiovascular event in the context of secondary preventative aspirin is greater with a meta-analysis of six studies with 50279 patients reporting withdrawal or non-adherence to aspirin associated with a three-fold higher risk of a major cardiac event (OR 2.14, 95% CI 1.75–5.61, $p=0.0001$). The OR increased to 89 (95% CI 29.9–269.6) in patients with stents. (37) A subsequent RCT including 156 patients showed that continuation of secondary prevention aspirin in UGIB was associated with significantly lower 8-week all-cause mortality despite a higher recurrent ulcer bleeding rate compared to placebo (1.3% vs 12.9%, difference 11.6%, 95% CI 3.7–19.5% and 10.3% vs 5.4%, difference 4.9% 95% CI -3.6–13.4% respectively). Given these findings, current guidelines suggest permanent discontinuation of aspirin for primary prevention should be considered. However, if used for secondary prevention, aspirin should be continued or, if stopped in severe UGIB, restarted after haemostasis is achieved (38,39).

Patients on dual antiplatelet therapy (DAPT) with recent placement of coronary artery stents are at high risk of stent occlusion if these med-

ications are held. While no RCTs exist in this area, a literature review identified 161 patients who had received DAPT and developed late or very late stent thrombosis. The median time to thrombosis was found to be seven days in the patient group that had discontinued both antiplatelet agents, but when aspirin was continued alone, the median time to event was 122 days (40). The British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy guidance suggest in close liaison with interventional cardiology colleagues that DAPT should be continued where possible (38). In the event of a major haemorrhage, the P2Y12 receptor antagonist should be stopped, and aspirin continued, with resumption dependent on rebleeding vs thrombosis risk but not more than five days.

Anticoagulants

Vitamin K antagonist (VKA) use is associated with a 3-fold increased risk of UGIB compared to the general population (41), with an age-standardised incidence rate of 5.8 per 1000 person a year (42). International normalised ratio (INR) is not associated with increased mortality (43), and in a case series of 233 patients with UGIB in which 97 (of the 102 anticoagulated patients) had an INR between 1.3–2.7, no difference in rebleeding rate after endoscopy was observed (23% vs 21%) (44). A single centre, retrospective review including 165 patients on VKA with a UGIB reported no difference in frequency of rebleeding, days in the hospital, transfusion requirement or in-hospital deaths in those supra-therapeutically anticoagulated (INR>4) compared to those with a therapeutic INR 2.0–3.9 (43). Given the apparent effectiveness of endotherapy even in the context of elevated INR, American guidelines advise that endotherapy in UGIB is reasonable with INR<2.5 (45). In severe UGIB with active bleeding or haemodynamic instability, guidelines advise temporarily suspending VKA and administering Vitamin K with a factor prothrombin complex. This is preferred to fresh frozen plasma due to reduced volume, faster onset of action and lack of requirement for blood group analysis (38,39,45).

Data on how the risk of UGIB with direct oral anticoagulants (DOACs) compares to VKA are limited. A retrospective cohort study including

92816 propensity score-matched patients on DOACs concluded the overall risk of UGIB was reduced in patients <65 years compared to VKA, with risk increasing after reaching this age (46). In the event of severe UGIB, adexanet alfa and idarucizumab can be utilised as reversal agents for selected DOACs. These medications are effective but are currently expensive, and there are concerns surrounding potential procoagulant effects (47). Unlike VKA, DOACs have short half-lives with effects lasting 12 to 24 hours. Caution is required in impaired renal function, which can reduce excretion rate, with dabigatran particularly susceptible, undergoing ~80% renal excretion (48). In non-life-threatening UGIB, European guidelines suggest that withholding the DOAC is usually sufficient (38).

A meta-analysis of 10 studies including 2080 patients resuming anticoagulation and 2296 patients discontinuing after GI bleeding showed that resumption of anticoagulation was associated with a significant reduction in thromboembolism and mortality (OR 0.340, 95% CI 0.178–0.652, $p=0.001$ and OR 0.499, 95% CI 0.419–0.595 $p<0.0001$ respectively) despite an increase in recurrent UGIB (OR 1.646, 95% CI 1.035–2.617 $p=0.035$) (49). European guidance for timing of the re-introduction of VKA is dependent on thrombotic risk. They recommend that lower thrombotic risk patients are recommenced on anticoagulation as soon as possible after seven days and higher-risk patients – within three days, preferably with heparin bridging (38). The basis for this advice is a retrospective study including 1329 patients, of whom 49.1% restarted warfarin following UGIB, which showed patients who restarted warfarin within seven days were at increased risk of recurrent bleeding while those who restarted warfarin after 30 days had increased risk of thrombo-embolic events (50). Due to the rapid onset of action (2 to 4 hours), caution should be taken reintroducing DOACs, which, in the absence of data, European guidelines suggest to be restarted as soon as possible after seven days (38).

Endoscopic therapies

The aetiology of bleeding at the time of endoscopy determines treatment, with several options now available to the endoscopist for the

management of UGIB. For non-variceal bleeding, these include injection of Epinephrine or a sclerosing agent, thermocoagulation (heater or gold probe, and argon plasma coagulation), mechanical therapy (clips) and topical haemostatic agents. All endoscopic therapies have been shown to reduce rebleeding rates compared to pharmacotherapy alone (51). Epinephrine injection (1:10000) can be utilised as a temporising measure, allowing improved visualisation of the bleeding point and application of a second modality, but should not be used as monotherapy (34). A Cochrane meta-analysis of 19 studies, including 2033 patients, reported that combination therapy (Epinephrine and another haemostatic technique) reduced the risk of further bleeding after haemostasis regardless of modality chosen compared to Epinephrine alone (RR 0.53, 95% CI 0.35–0.81) (52).

Over the last decade, interest in the endoscopic use of topical haemostatic powders or gels for UGIB has increased. These agents include small mineral granule TC-325, starch-derived polysaccharide haemostatic system and synthetic self-assembling peptide agents. Initial data on these agents were limited to case series, although cohort, registry studies, and pilot RCTs are now available. A meta-analysis of 59 studies, including 3417 patients with variceal bleeding, which was published this year, reported that immediate haemostasis was achieved in 93% (95% CI 89–95%) when used as primary therapy and 90% (95% CI 85–93%) as rescue therapy. The overall rebleeding rate was 18% (95% CI 15–21%) (53). Another recently published meta-analysis compared TC-325 to standard endoscopic therapy (SET) and included 362 patients across 5 RCTs in non-variceal UGIB. No difference was observed in primary haemostasis (RR 1.09, 95% CI 0.95–1.25, $p=0.20$); however, failure to achieve haemostasis (defined as recurrent bleeding up to 30 days from index endoscopy) was seen in the SET group (RR 0.30, 95% CI 0.12–0.77, $p=0.01$) (54). Topical agents appear effective at instigating haemostasis (Figure 1); however, currently, they are considered a temporary measure by the European Society of Gastrointestinal Endoscopy that should be considered in patients with persistent bleeding refractory to standard modalities (7).



Figure 1. A large posterior duodenal ulcer bleeding at the time of endoscopy treated with Epinephrine and through the scope clips. Ongoing oozing despite dual therapy; therefore, topical haemostatic powder is applied with good effect

Endoscopic management of variceal bleeding depends on the location within the upper gastrointestinal tract. Oesophageal varices are treated with variceal band ligation, which reduces mortality and rebleeding compared to sclerotherapy (55). Though less common than oesophageal varices, gastric varices have poorer outcomes (56). Gastroesophageal varices extending 2–5cm along the lesser curve of the stomach can be managed with band ligation, while injection therapy of thrombin or tissue adhesive is recommended for the remainder (20,57). Despite concerns regarding using an exogenous substance with the potential for embolization and infection, tissue adhesive injection has been shown to be effective for the obturation of varices with a low complication rate (58). Thrombin has also been utilised to manage gastric varices, with case series reporting it safe and effective for therapeutic use (59,60). A recent small RCT suggested that thrombin has similar efficacy to tissue adhesive but has fewer complications (61).

Post-endoscopic pharmacological management

Non-variceal management

PPI administration is effective following endoscopy for lesions that require endo-therapeutic intervention or have high-risk stigmata for rebleeding. A meta-analysis comparing high-dose PPI and placebo showed a significant reduction in rebleeding and mortality (RR 0.40, 95% CI 0.28–0.59 and 0.41, 0.20–0.84 respectively) (62). Although it is typically administered intravenously with an initial bolus followed by a subsequent infusion, recent guidelines have suggested that IV bolus or high-dose oral PPI alone may also be considered (7). A meta-analysis of 13 studies showed that intermittent PPI use was non-inferior to continuous intravenous infusion (RR of rebleed within seven days 0.72, upper boundary of one-sided 95% confidence interval 0.97) (63). An earlier study comparing the effect of intravenous PPI and oral PPI on stomach pH over 24 hours showed they were comparable with a pH >6 for 67.8% of the period with intravenous PPI and 64.8% with oral PPI (difference 3.0%, 95% CI -9.2–15.2%) (64).

Following initial PPI management, patients with high-risk lesions requiring endotherapy can be commenced on a two-week course of high-dose, oral PPI (8) twice a day with an RCT. Two hundred ninety-three patients showed a reduced rebleeding rate compared to the standard dose (10.8% vs 28.7%, $p=0.002$) (65). After this course, a further 2–4 weeks of PPI once a day can be administered (34).

The testing for *H pylori* by rapid urease test or biopsy at the time of UGIB in the context of peptic ulcer disease has shown low sensitivity (66), and delayed eradication therapy can increase the risk of recurrent bleeding. A Swedish cohort study including 29032 patients receiving *H pylori* eradication therapy showed higher rates of recurrent and complicated ulcers in those who received eradication therapy within 8–30 days of peptic ulcer diagnosis compared to those who received it for seven days (HR 1.17 (95% CI 1.08–1.25 and 1.55, 1.35–1.78 respectively). In the same study, the risk of recurrence or complicated ulcer with delay in treatment continued to increase with time, up to 365 days (67).

Based on these findings, European guidelines advise that in the event of a negative H pylori test at index endoscopy, testing should be repeated within four weeks (7).

Concerns regarding the potential interaction between concomitant PPI and clopidogrel use have been raised. Clopidogrel is a prodrug that requires metabolism by a number of cytochrome P450 enzymes, including CYP2C19, which is inhibited by PPI. Several small studies suggested significantly reduced efficacy of clopidogrel in the context of PPI (68,69) use, potentially increasing the risk of cardiac events. A retrospective Italian cohort study including 3896 patients estimated that hospitalisation for acute coronary syndrome occurred in 15% of patients taking clopidogrel and PPI vs 3.4% in those on clopidogrel without PPI ($p < 0.001$) at 1-year follow-up post discharge with low-risk GI bleeding (70). However, these findings were challenged by the Clopidogrel and the Optimisation of Gastrointestinal Events Trial (COGENT). This large double-blinded RCT, including 3761 patients on dual antiplatelet therapy, showed that prophylactic use of PPI reduced the rate of gastrointestinal events significantly at 180 days (event rate 1.1% with omeprazole vs 2.9% with placebo hazard ratio 0.13, 95% CI 0.18–0.63, $p < 0.001$). No significant difference in cardiovascular events was observed between groups. It should be noted this study ended prematurely due to sponsorship withdrawal but was still able to report (71).

Variceal management

As noted above, using vasoactive medication as an adjunct to endoscopic band ligation significantly reduces rebleeding rates, though this did not translate into improved 30-day mortality (72,73). Where variceal bleeding is confirmed at endoscopy, vasoactive medications should be continued for 2–5 days (19,20,31). Bacterial infection is common in cirrhotic patients presenting with UGIB and has been shown to increase the risk of rebleeding (74). Patients with cirrhosis may not manifest the usual clinical signs of infection, and prophylactic antibiotics should be continued for up to 7 days (20).

There has been increased interest in the use of longer-term Carvedilol as the optimal non-se-

lective Beta blocker for primary and secondary prevention of variceal bleeding, with evidence of improved haemodynamic and clinical outcomes with Carvedilol compared with other therapies (75,76).

In conclusions: UGIB remains a common cause of emergency hospitalisation and has been extensively studied, leading to improvement in pre-endoscopic resuscitation, endo-therapeutic techniques and pharmacological intervention. PPI use for higher-risk non-variceal bleeding has been shown to decrease rebleeding and mortality. Despite its widespread effective use in surgery and trauma, Tranexamic acid has been shown not to improve outcomes in UGIB and is associated with increased thromboembolic events. In the context of variceal bleeding, early use of vasoactive medication and antibiotics improves clinical outcomes. These pharmacological advances have helped improve the management of UGIB, but challenges remain. The increased use of antithrombotic agents in ageing comorbid populations has created additional complexity, with the need to balance bleeding and thrombotic risks. Further research is required in this area to optimise patient management.

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