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Management of non-variceal upper gastrointestinal tract hemorrhage: Controversies and areas of uncertainty

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Abstract

Upper gastrointestinal tract hemorrhage (UGIH) remains a common presentation requiring urgent evaluation and treatment. Accurate assessment, appropriate intervention and apt clinical skills are needed for proper management from time of presentation to discharge. The advent of pharmacologic acid suppression, endoscopic hemostatic techniques, and recognition of *Helicobacter pylori* as an etiologic agent in peptic ulcer disease (PUD) has revolutionized the treatment of UGIH. Despite this, acute UGIH still carries considerable rates of morbidity and mortality. This review aims to discuss current areas of uncertainty and controversy in the management of UGIH. Neoadjuvant proton pump inhibitor (PPI) therapy has become standard empiric treatment for UGIH given that PUD is the leading cause of non-variceal UGIH, and PPIs are extremely effective at promoting ulcer healing. However, neoadjuvant PPI administration has not been shown to affect hard clinical outcomes such as rebleeding or mortality. The optimal timing of upper endoscopy in UGIH is often debated. Upon completion of volume resuscitation and hemodynamic stabilization, upper endoscopy should be performed within 24 h in all patients

with evidence of UGIH for both diagnostic and therapeutic purposes. With rising healthcare cost paramount in today's medical landscape, the ability to appropriately triage UGIH patients is of increasing value. Upper endoscopy in conjunction with the clinical scenario allows for accurate decision making concerning early discharge home in low-risk lesions or admission for further monitoring and treatment in higher-risk lesions. Concomitant pharmacotherapy with non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents, such as clopidogrel, has a major impact on the etiology, severity, and potential treatment of UGIH. Long-term PPI use in patients taking chronic NSAIDs or clopidogrel is discussed thoroughly in this review.

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Key words: Hemorrhage; Proton pump inhibitors; *Helicobacter pylori*; Prokinetic agents; Hemostasis; Thienopyridines

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INTRODUCTION

Fundamental changes have occurred over the past several decades in the management of upper gastrointestinal tract hemorrhage (UGIH). Pharmacologic gastric acid suppression, recognition of *Helicobacter pylori* (*H. pylori*) as a causative agent in peptic ulcer disease, and the wide-

Table 1 Sensitivity, specificity, positive predictive value and negative predictive value for death and rebleeding using 6 common upper gastrointestinal tract hemorrhage scoring systems

Scoring system	Death	Rebleeding
Pre-endoscopy Rockall risk score		
Sensitivity	100 (43.8-100)	69.6 (49.1-84.4)
Specificity	18.5 (14.8-22.9)	17.5 (13.8-22.0)
PPV	1.0 (0.4-3)	5.5 (3.4-8.8)
NPV	100 (94.4-100)	89.2 (79.4-94.7)
Post-endoscopy Rockall risk score		
Sensitivity	33.3 (6.1-79.2)	87.0 (67.9-95.5)
Specificity	29.6 (25.1-34.6)	31.1 (26.4-36.3)
PPV	0.4 (0.1-2.2)	8.1 (5.3-12.1)
NPV	98.1 (93.4-99.5)	97.2 (92.0-99.0)
Blatchford scoring system		
Sensitivity	100 (83.89-100)	94.29 (81.40-98.42)
Specificity	1.83 (0.71-4.61)	0.98 (0.27-3.50)
PPV	8.51 (5.58-12.79)	14.04 (10.17-19.06)
NPV	100 (51.01-100)	50.00 (15.00-85.00)
Forest classification		
Sensitivity	85.00 (63.96-94.76)	71.43 (54.95-83.67)
Specificity	50.23 (43.66-56.79)	50.49 (43.68-57.28)
PPV	13.49 (8.6-20.54)	19.84 (13.81-27.65)
NPV	97.35 (92.49-99.10)	91.15 (84.77-95.12)
Cedars-Sinai Medical Center predictive index		
Sensitivity	95.00 (76.39-99.11)	80.00 (64.11-89.96)
Specificity	41.55 (35.22-48.17)	41.67 (35.12-48.53)
PPV	12.93 (8.44-19.31)	19.05 (13.52-26.15)
NPV	98.91 (94.09-99.81)	92.39 (85.12-96.26)
Baylor College scoring system		
Sensitivity	87.50 (52.91-97.76)	30.77 (12.68-57.63)
Specificity	58.49 (45.09-76.74)	47.92 (34.47-61.67)
PPV	24.14 (12.22-42.11)	13.79 (5.50-30.56)
NPV	96.88 (84.26-99.45)	71.88 (54.63-84.44)

95% confidence intervals are recorded in parentheses. PPV: Positive predictive value; NPV: Negative predictive value.

spread dissemination of flexible endoscopy and endoscopic hemostatic techniques have contributed to a paradigm shift in the treatment of complicated peptic ulcer disease, in particular, from predominantly surgical to predominantly endoscopic management. At the same time, an increasing proportion of patients presenting with UGIH are older or elderly patients^[1], and a significant number of patients with UGIH consume non-steroidal anti-inflammatory drugs (NSAIDs) and/or antiplatelet therapy to treat other medical comorbidities. Given the confluence of these factors, UGIH continues to have a considerable impact with respect to patient morbidity and mortality, as well as health care resource utilization. The annual incidence of UGIH has been estimated as low as 48 and as high as 165 cases per 100 000 population, and the mortality rate remains high somewhere between 7% and 14%^[2-6]. UGIH accounts for > 300 000 annual hospitalizations in the United States, with an estimated cost of \$2.5 billion^[3,5]. This article aims to review the management of UGIH, with an emphasis on discussion of areas of controversy or uncertainty in current practice.

INITIAL ASSESSMENT

By definition, UGIH originates proximal to the ligament of Treitz. UGIH accounts for the preponderance of all gastrointestinal hemorrhage; estimated at 4-6 times more common than lower gastrointestinal (GI) hemorrhage^[7]. Initial assessment of the pace and acuity of the bleeding episode has major bearing on the initial management of UGIH. For patients presenting with UGIH and evidence of hemodynamic compromise, the fundamental goal of initial management is adequate and appropriate volume resuscitation. Additional stratification of patients into high- and low-risk categories may be based on clinical and endoscopic criteria^[8]. Predictors of poor prognosis include: age > 65 years, shock, poor overall health, comorbid conditions, low initial hemoglobin/hematocrit, active bleeding (red blood per rectum or hematemesis), sepsis, and elevated creatinine or serum transaminases^[2,8,9]. Several scoring systems have been created and/or validated for this purpose, including APACHE II, Forrest Classification, Blatchford, pre-endoscopic Rockall, Baylor College, Cedars-Sinai Medical Center and Rockall indexes (Table 1 compares 6 commonly used scoring systems)^[10,11]. Some of these may be cumbersome (APACHE II) or require data not immediately available based on initial clinical assessment (the Rockall Scoring System, for instance, requires endoscopic data) and therefore may be of limited utility in the acute setting^[12].

The role of nasogastric tube placement and aspirate inspection in the initial assessment of UGIH has fallen out of favor in many emergency room and acute care settings. In theory, the presence of bright red blood *via* nasogastric aspirate suggests active UGIH and should prompt urgent esophagogastroduodenoscopy (EGD)^[3]. The absence of blood on nasogastric aspirate, however, does not exclude the presence of a culprit UGIH source. In a study by Aljebreen *et al*^[13], 15% of patients with UGIH and clear or bilious nasogastric aspirate were ultimately found to have an underlying high risk lesion during EGD.

PHARMACOLOGIC THERAPY PRIOR TO ENDOSCOPY

Pharmacologic gastric acid suppression has changed the face of peptic ulcer disease (PUD) treatment, both by favoring hemostasis in the short term (platelet aggregation and clot formation are impaired at acidic gastric pH^[14]), and enabling ulcer healing and remission over the longer term^[3]. Proton pump inhibitors (PPIs) covalently bind to and inhibit the H-K ATPase pump of the gastric parietal cells, thus inhibiting the final common pathway of acid secretion. PPIs offer more durable and sustained acid suppression than histamine receptor antagonists, which are prone to tachyphylaxis^[15]. For these reasons, PPIs have become the dominant acid suppressive therapy used in the treatment of UGIH.

An emerging area of importance is the optimal dose, route of administration, and timing of PPI therapy in patients presenting with UGIH. Administration of neoadjuvant PPI, prior to diagnostic endoscopy or endoscopic therapy, has become widespread, and this practice recommendation has been supported by consensus guidelines^[2]. This approach may be particularly reasonable in instances when access to prompt EGD and/or availability of endoscopic therapeutic expertise is limited. Otherwise, however, it is uncertain whether neoadjuvant PPIs confer benefit with respect to meaningful clinical outcomes. In a controlled prospective study of patients with UGIH randomized to intravenous PPI *vs* placebo prior to endoscopy^[16], patients in the PPI arm were less likely to have active bleeding at the time of endoscopy and to require endoscopic hemostatic therapy. There was no difference in transfusion requirements, rates of rebleeding, requirement for surgery, or 30-d mortality when comparing patients receiving PPIs to those receiving placebo. A systematic meta-analysis, based on published controlled data in the medical literature, reported no benefit of neoadjuvant (pre-endoscopic) PPI therapy on rates of rebleeding, salvage surgery for failures of endoscopic hemostasis, or mortality^[17].

Adjuvant PPI therapy, administered following diagnostic and/or therapeutic EGD, has been proven effective, as well, leading to a decrease in recurrent PUD bleeding, need for blood transfusion, need for surgery, and duration of hospital stay^[3,18,19]. Despite these major impacts, studies have not demonstrated an impact of PPIs on mortality due to UGIH^[3,20,21]. Furthermore, whether in the neoadjuvant or adjuvant setting, the optimal dosing, route of administration, and duration of post-endoscopy PPI has not been clearly established. Current guidelines recommend the use of high-dose intravenous PPI therapy for 3 d following successful endoscopic hemostasis^[2]. In many studies, high-dose PPI therapy is defined as an initial bolus (omeprazole 80 mg) followed by continuous infusion (omeprazole 8 mg/h) for up to 72 h. However, there has been limited direct comparison of this high-dose intravenous regimen in comparison to alternative regimens. Whether continuous intravenous infusion of PPIs is clearly superior to intermittent bolus dose is uncertain; similarly, whether intravenous PPIs are clearly superior to highly bioavailable oral PPIs in patients able to take oral medications is uncertain.

TIMING OF ENDOSCOPIC EVALUATION

Endoscopic evaluation is an essential part of UGIH management. Urgent EGD has been proposed as the standard of care in patients with high-risk lesions, although the precise timing of urgent EGD has been variably defined. American Society for Gastrointestinal Endoscopy practice guidelines for the treatment of non-variceal UGIH suggest that early endoscopy (within 24 h) maximizes the impact on hospital length of stay and transfusion requirements, yet do not make formal recommendations regarding the optimal time for performing EGD within this 24-h window^[22].

In theory, the availability both of on-call physicians proficient in endoscopic hemostasis and on-call support staff with technical expertise in usage of endoscopic devices enable performance of EGD on a 24-h/7-d basis. Several studies have examined the timing of upper endoscopy and resultant impact on both patient outcomes and resource utilization. In a study by Sarin *et al*^[23], a retrospective review of > 500 patients who underwent upper endoscopy for non-variceal UGIH, the timing of endoscopy was stratified into three categories: < 6 h, 6-24 h and > 24 h. There was no significant difference in mortality or need for surgery between the < 6 h and 6-24 h groups. However, there was a difference between the two < 24 h groups and the > 24 h group. These findings were supported by a more recent retrospective review in 2007 that examined 169 patients with acute non-variceal UGIH with either systolic blood pressure < 100 mmHg or heart rate > 100 beats/min on presentation. Patients were divided into two groups: those who received endoscopy within 6 h *vs* 6-24 h. Again, there were no significant differences between the groups in any of the primary outcomes, including rebleeding, need for surgery, in-hospital mortality, or hospital readmission within 30 d^[24].

In a variation on this theme, Dorn *et al*^[25] have examined the difference in clinical outcomes among patients admitted for UGIH on either a weekday or a weekend. Those admitted on a weekend had a slight but significant increase in mortality (hazard ratio of 1.09), hospital length of stay, and hospitalization cost. Although the weekend patients waited longer for EGD than their weekday counterparts, the entire effect on patient outcomes could not be accounted for by the delay in endoscopy timing alone. Further study is needed to elicit other potential causes of this weekend effect. Our practice is to perform EGD as soon as is feasible following hemodynamic resuscitation and stabilization of the patient, and within 12 h of clinical presentation.

In addition to offering hemostatic techniques to prevent continued or recurrent bleeding, a major benefit of endoscopy is the ability to risk stratify the lesion and triage patients to those who require inpatient or more intensive monitoring, *vs* those who are candidates for early hospital discharge. With respect to peptic ulcer hemorrhage, lesions at high risk for recurrent bleeding include ulcers > 2 cm, or ulcers with active bleeding, a visible vessel, or adherent clot. Such lesions warrant both endoscopic therapy, when feasible, and inpatient monitoring post-endoscopy. Conversely, clean-based ulcers or ulcers with flat pigmented spots are considered low risk and do not require endoscopic therapy^[26], and patients found to have such low-risk lesions may be candidates for early discharge, even from an emergency room setting.

Much improvement in current management of UGIH and resource allocation for treatment of UGIH could be achieved in this area. Numerous studies have shown that early endoscopy is not often followed by early discharge of appropriate low-risk patients. Bjorkman *et al*^[27] have shown that EGD within 6 h of presentation to the emergency department versus 48 h did not change hospital utilization of resources, the study's primary endpoint. In

Table 2 Areas requiring further investigation

Pharmacologic therapy prior to endoscopy	Determine optimal route and dosage of PPI in UGIH (continuous infusion <i>vs</i> intermittent IV bolus <i>vs</i> oral dosing)
Timing of endoscopic evaluation	Defining optimal timing of initial endoscopy, implementation of early discharge in low risk patients
Prokinetic agents as endoscopic adjuncts	Clearly define the role for prokinetics in UGIH with randomized controlled trials, specifically define the optimal agent, dose and timing prior to endoscopy
Long-term PPI management	Clarification of potential long-term sequelae of PPI including: osteoporosis, <i>C. difficile</i> infection and community-acquired pneumonia
PPI and thienopyridines	Consensus on the clinical importance of this interaction, a complete randomized controlled trial to support the truncated COGENT trial data
<i>H. pylori</i> and UGIH	<i>H. pylori</i> testing that allows accurate test results in the setting of acute UGIH

PPI: Proton pump inhibitor; *H. pylori*: *Helicobacter pylori*; UGIH: Upper gastrointestinal tract hemorrhage; IV: Intravenous; COGENT: Clopidogrel and the optimization of gastrointestinal events trial.

a recently published study, Chaparro *et al*^[28] have formulated an early discharge algorithm using retrospective data and then examined this algorithm in a prospective cohort. Even at their institution using their algorithm, only 13/29 (45%) low-risk patients were discharged early. In view of these data, there is much room for improvement in clinical practice surrounding implementation of practice guidelines concerning early hospital discharge of low-risk UGIH patients and achieving the potential health care cost savings. Table 2 illustrates other areas in need of further investigation and improved recommendations.

CHOICE OF ENDOSCOPIC HEMOSTATIC TECHNIQUE

Endoscopic therapies employed in the treatment of UGIH include: (1) pharmacologic therapies, including injection of epinephrine, sclerosants and even normal saline; (2) coagulation therapies, including monopolar or bipolar cautery and argon plasma coagulation; and (3) mechanical tamponade, including hemoclips and bands. Each of these therapies has demonstrated efficacy in different clinical settings. Often, the choice of which endoscopic therapy to employ is a clinical judgment based on provider preference and expertise.

Available data suggest that epinephrine injection plus a second endoscopic intervention is superior to epinephrine injection alone. Calvet *et al*^[29] completed a systematic review and meta-analysis in 2004 which included 16 studies and > 1600 patients with UGIH secondary to PUD, and who underwent endoscopic therapy with epinephrine alone or epinephrine plus a second hemostatic modality. Adding an adjunct therapy reduced the rebleeding rate from 18.4% to 10.6% [odds ratio (OR): 0.53, 95% CI: 0.40-0.69], reduced the need for emergency surgery from 11.3% to 7.6% (OR: 0.64, 95% CI: 0.46-0.90), and reduced mortality from 5.1% to 2.6% (OR: 0.51, 95% CI: 0.31-0.84). Vergara *et al*^[30] have confirmed these findings in a recent Cochrane review (2008). Rebleeding, need for surgical intervention, and mortality were all lower in groups receiving dual therapy. Additionally, there was no increased risk of significant complications or adverse events when dual therapy was used. In the above studies

and reviews, endoscopic therapy is usually reserved for high-risk lesions (active bleeding and visible vessels). Jensen *et al*^[31] have additionally defined a role for removal of adherent clots in the treatment of PUD bleeding. In one study, removal of adherent clot and treatment with a second endoscopic intervention resulted in lower rebleeding rates when compared to not removing the adherent clot (35% *vs* 0%).

Even when endoscopy fails to provide durable and definitive hemostasis, endoscopy may provide a beneficial role in localization of the bleeding lesion to target salvage non-endoscopic intervention. Repeat endoscopy can assist both interventional radiology and/or surgery in the event that bleeding continues or recurs and alternative management is necessitated. Second-look endoscopy has also been shown to improve rebleeding rates in certain clinical situations, but without improvement in the need for surgery or mortality^[3]. Current guidelines do not support routine use of second-look endoscopy.

PROKINETIC AGENTS AS ENDOSCOPIC ADJUNCTS

The presence of retained blood in the UGI tract can limit the ability to identify definitively a bleeding source and/or deliver endoscopic hemostatic therapy. Prokinetic agents may promote UGI tract motility and facilitate gastric emptying of retained blood prior to endoscopy; however, the use of such agents may be highly physician dependent. American Society for Gastrointestinal Endoscopy guidelines^[22] indicate that the use of erythromycin, when administered intravenously prior to EGD, may improve mucosal visibility. A recent meta-analysis published in *Gastrointestinal Endoscopy*^[32] has shown that either erythromycin or metoclopramide given prior to endoscopy significantly reduced the need for repeat endoscopy to identify the bleeding source. However, use of a prokinetic agent led to no identifiable impact on total units of blood transfused, hospital stay, or need for surgical intervention^[33]. As was germane to the discussion of pre-endoscopic PPI therapy, if there is a role of prokinetic agents in the endoscopic diagnosis and management of UGIH, the optimal agent,

dose and timing prior to endoscopy have not been defined. Metoclopramide has been assigned a “black box warning” by the United States Food and Drug Administration (FDA) due to risk of neurologic side effects, and caution should therefore be advised with use of this agent.

LONG-TERM PPI MANAGEMENT

PPIs are recommended for 6-8 wk following UGIH and/or endoscopic treatment of PUD to allow for full mucosal healing. Several studies have shown a therapeutic benefit of PPIs in patients using NSAIDs chronically and/or patients with confirmed *H. pylori* infection^[34,35]. After initial mucosal healing has been achieved, is there a benefit to long-term PPI use for secondary prophylaxis? Studies have shown that in patients who have PUD complicated by bleeding, there is a 33% risk of rebleeding in 1-2 years. Furthermore, there is a 40%-50% rebleeding risk over the subsequent 10 years following the initial episode of bleeding^[13]. Randomized prospective trials have demonstrated a benefit to long-term acid-suppression therapy in two settings: chronic NSAID users and *H. pylori*-infected patients. As demonstrated in a 2001 *New England Journal of Medicine* article by Chan *et al.*^[34], in patients taking NSAIDs other than acetylsalicylic acid (ASA) who were concomitantly infected with *H. pylori*, omeprazole provided added protection above bacterial eradication alone.

Although beneficial in both treatment and prevention of UGIH, PPI therapy is not without potential risks. Chronic PPI therapy has been associated with *Clostridium difficile* infection, community-acquired pneumonia, and calcium malabsorption resulting in osteoporosis and increased fracture risk^[36]. These associations have originated largely from observational studies and no strong data exist to link PPI therapy directly as a causative factor in any of these outcomes. However, given these potential sequelae, long-term PPI therapy should only be used when justified by a clear medical indication^[2].

PPIS AND THIENOPYRIDINES

Much recent attention has surrounded the concomitant use of PPIs and thienopyridines, particularly clopidogrel. This has included an FDA warning regarding combined use of these medications^[36]. *In vitro* studies have suggested that omeprazole, which is metabolized predominately through the CYP2C19 isoenzyme of cytochrome P450, inhibits conversion of clopidogrel, a prodrug, to its active form, thus reducing its therapeutic margin^[37]. Most of the original data were specific to omeprazole and subsequent experiments using pantoprazole, lansoprazole and esomeprazole have not shown an equal class effect^[3,37,38]. Additionally, although a measurable change in platelet function occurred in patients concomitantly taking PPIs and clopidogrel, the data were mixed with regards to clinically significant cardiovascular outcomes.

Subsequent retrospective reviews and observational studies have attempted to define the true impact of PPIs on the therapeutic index of thienopyridines, but with mixed results. The French Omeprazole CLopidogrel As-

pirin study measured vasodilator-stimulated phosphoprotein phosphorylation; a measure of the inhibitory effect of clopidogrel on platelets *in vivo*. Patients taking both 75 mg ASA and 75 mg clopidogrel daily were randomized to either 20 mg omeprazole or placebo daily. One hundred and twenty-four patients were included and the results showed an 11.6% decrease in platelet inhibition by clopidogrel among those randomized to omeprazole, but no clinical outcomes were measured^[38]. The TIMI Study Group at Brigham and Women's Hospital in Boston have attempted to clarify the link between *in vitro* interactions, measures of platelet function, and clinical outcomes in patients on either of the thienopyridines and PPIs through the analysis of two trials: prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation-TIMI 44, the primary endpoint of which was inhibition of platelet aggregation at 6 h, and trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-TIMI 38, with a primary composite endpoint of cardiovascular death, myocardial infarction or stroke. The first study demonstrated a reduction in the inhibitory effect of thienopyridines on platelet aggregation in patients taking PPIs after loading doses of either clopidogrel (12% decrease) or prasugrel (7.1% decrease). However, in the second trial, > 13 000 patients with acute coronary syndrome were randomized to prasugrel or clopidogrel, of which 33% of 4500 patients were on PPIs at randomization. PPI was continued without change in dosing or frequency. There was no association between PPI use and the primary endpoint, a composite cardiovascular event^[39]. Additionally, when the data were assessed by specific PPI (omeprazole, lansoprazole, pantoprazole or esomeprazole), there was no correlation.

Most recently, the only prospective randomized controlled trial to address this important clinical question, the Clopidogrel and the optimization of gastrointestinal events trial (COGENT) Trial, was published in the *New England Journal of Medicine*. COGENT randomized patients with an indication for dual antiplatelet therapy to clopidogrel 75 mg plus omeprazole 20 mg daily or clopidogrel alone. In addition, every patient was given either 81 or 325 mg enteric coated aspirin. The primary cardiovascular endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, revascularization, or stroke. Over 3700 patients were included in the final analysis of events at 180 d after randomization. There were 109 cardiovascular events; 4.9% in the clopidogrel plus omeprazole arm, and 5.7% in the clopidogrel plus placebo arm (HR: 0.99; 95% CI: 0.68-1.44). The primary gastrointestinal endpoint was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction or perforation. There were 51 gastrointestinal events; 1.1% in the clopidogrel plus omeprazole group, and 2.9% in the clopidogrel plus placebo arm (HR: 0.13; 95% CI: 0.03-0.56)^[40]. These data suggest no association between omeprazole and clinically meaningful adverse cardiovascular outcomes when used in conjunction with clopidogrel. However, there was a significant reduction in adverse gastrointestinal events in patients receiving omeprazole. A significant limitation of this study

was premature study termination due to loss of funding, thereby attenuating the statistical power of the study.

The ambiguity of this matter is further demonstrated in the following consensus statements. The American College of Cardiology Foundation/American College of Gastroenterology (ACG)/American Heart Association (AHA) joint guidelines released in 2008 state, "In the interest of patient safety, the AHA/ACC and the ACG advise that patients who are currently taking these medications should not change their medication regimen unless advised by their healthcare provider". A revised joint statement was released in December 2010 stating, "Pharmacokinetic and pharmacodynamic studies, using platelet assays as surrogate endpoints, suggest that concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. The strongest evidence for an interaction is between omeprazole and clopidogrel. It is not established that changes in these surrogate endpoints translate into clinically meaningful differences. Observational studies and a single randomized clinical trial have shown inconsistent effects on (cardiovascular) outcomes of concomitant use of thienopyridines and PPIs. A clinically important interaction cannot be excluded, particularly in certain subgroups, such as poor metabolizers of clopidogrel. The roles of either pharmacogenomic testing or platelet function testing in managing therapy with thienopyridines and PPIs has not yet been established"^[41].

NON-ACID DIRECTED PHARMACOLOGIC THERAPY

The role of *H. pylori* in PUD has been clearly elucidated over the years, beginning with Marshall and Warren's pioneering work. Since that time, many studies have demonstrated the beneficial effects of *H. pylori* eradication in the treatment of PUD. In a 1997 *Lancet* study, Chan *et al.*^[34] reported that clearance of *H. pylori* in patients taking naproxen for 8 wk, irrespective of PPI use, significantly reduced the presence of PUD at time of repeat endoscopy: 26% *vs* 70%. Current guidelines support the test and treatment mantra for *H. pylori* in the setting of UGIH^[2]. However, the appropriate timing of *H. pylori* testing is unclear given the potential for false-negative test results in the setting of in the setting of UGIH and false negative results due to PPI use. In a 2001 study by Griño *et al.*^[42], 78 patients with endoscopically documented UGIH secondary to PUD underwent diagnostic testing for *H. pylori* in the acute setting by one of four modalities: histology, rapid urease test, urea breath test and serology. The sensitivity/specificity for each respective diagnostic test was as follows: 48.5/100 for the rapid urease test, 91/77.8 for the breath test, 89.5/80 for serology and 86.3/100 for histology. Additional support for questioning immediate *H. pylori* test results was provided by Guell *et al.*^[43], who have reported a 79% false-negative rate with rapid urease testing and a maximum sensitivity of only 86% if both a rapid urease test and histological examination were performed on each biopsy specimen. Based on these data, a recommendation to retest at a later date all patients with negative immediate *H. pylori* test in the setting of acute UGIH may be reasonable^[42-44].

CONCLUSION

UGIH requires early and accurate assessment, triage and resuscitation, in addition to well-coordinated care between generalist and sub-specialist to maximize patient outcomes. All patients with UGIH need upper endoscopy within 24 h of presentation to characterize further and potentially treat the bleeding source. Epinephrine plus a second modality of endoscopic therapy has proven superior to epinephrine alone. *H. Pylori* infection should be confirmed and treated when present. Negative *H. pylori* test in the acute setting should be followed by repeat testing to avoid false-negative results and minimize the risk of recurrent bleeding. Appropriate duration of PPI therapy is of critical importance to allow mucosal healing and to prevent rebleeding in the high-risk patient. Current data do not support a meaningful clinical interaction between PPIs and thienopyridines. Future clinical and research attention to the issues addressed in this review may serve to resolve current areas of uncertainty and controversy, and optimize clinical outcomes for patients presenting with UGIH.

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