Philippine Consensus Statements on the Management Of Non-Variceal Upper Gastrointestinal Bleeding: 2012

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Background

Peptic ulcer disease (PUD) remains common in many parts of the Asia-Pacific region in spite of an overall decrease in incidence and prevalence worldwide. Several population-based studies from the US and Europe showed annual incidence rates of 0.10–0.19% for physician-diagnosed PUD, and 0.03–0.17% for hospital-based diagnosis. The annual prevalence rates have similarly decreased based on physician diagnosis at 0.12–1.50% and 0.10–0.19% for hospital-based diagnosis.[1,2] In Malaysia, the overall prevalence of duodenal ulcer (DU) decreased significantly from 21.1% in 1989–1990 to 9.5% in 1999–2000 ($p < 0.001$). Similarly, the prevalence of gastric ulcer (GU) decreased from 11.9% to 9.4% ($p < 0.001$).[3] In the Philippines, peptic ulcer prevalence decreased significantly over a seven-year period, i.e., from 35.87% in 1996 to 18.80% in 2002; although the prevalence of peptic ulcer bleeding remained stable. This decline was noted in both GU and DU (20.05 vs 14.34%, and 15.83 vs 7.02%, respectively), and was attributed largely to the decrease in H. pylori-associated PUD.[4]

Parallel to the decrease in PUD prevalence, complications from PUD such as upper gastrointestinal (GI) bleeding have also diminished. In the Netherlands, the incidence of upper GI bleeding significantly decreased from 61.7/100,000 in 1993 and 1994 to 47.7/100,000 in 2000.[5] In Sweden, there is a significant decrease in ulcer complications in both sexes after 1988. Incidence rates fell from 7.8 to 1.5 per 100,000 population for perforated peptic ulcer and 40.2 to 5.2 for peptic ulcer bleeding.[6] A population-based study from Italy similarly reported a decreasing incidence from 112.5 to 89.8 per 100,000 population over a two-year period corresponding to an overall decrease of approximately 35.5% (95% CI, 24.2%-46.8%). Overall mortality decreased from 17.1 to 8.2 per 100,000/year, which corresponded to a 60.8% decrease after adjustment for age (95% CI, 46.5%-75.1%).[7]

Although H. pylori-associated PUD is decreasing in many regions of the world, an increasing proportion of current ulcer bleeding episodes appear to be related to the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).[8,9,10] Prescriptions of drugs known to cause PUD, such as aspirin and NSAIDs, have increased over the same time period[6,11] and strategies for the prevention of NSAID-induced PUD, e.g., gastroprotection, remains far from optimal.[12,13] As a result, NSAID-induced peptic ulcer bleeding remains a major cause for hospitalization and emergency interventions. Hospital admission rates for PUD complications increased in women between 1980 and 2003, from 4.8 to 9.1 per 100,000 in 1994, and 6.5 per 100,000 in 2003.[14] An endoscopy-based study from Rotterdam noted an increasing incidence of complicated ulcers for both duodenal and gastric ulcers, an increasing age at diagnosis for patients with duodenal ulcers in spite of a declining incidence of H. pylori-positive ulcers. Active bleeding (Forrest 1) was seen in 6.5% of all duodenal ulcers and 3.9% of all gastric ulcers, and signs of bleeding (i.e., a visible vessel (Forrest 2a), an overlying clot (Forrest 2b) or a hematin-covered base (Forrest 2c)) were diagnosed in 16.2% of the duodenal ulcers, and 9.0% of the gastric ulcers.[15] In Finland, the incidence of elective operations for PUD decreased by 89% over a 25-year period (1972-1999). However, there was a 44% increase in emergency operations for PUD, particularly among older women with bleeding gastric ulcers.[16]

Prompt recognition and improvements in diagnosis and non-operative treatments of non-variceal upper gastrointestinal bleeding (NVUGIB) during the last three decades have contributed to a reduction in mortality, albeit not substantially. An Italian population-based study reported that over a two-year period, overall mortality decreased from 17.1 to 8.2 per 100,000 per year, corresponding to a 60.8% decrease after adjustment for age (95% CI, 46.5%-75.1%). The age standardized mortality rate for ulcer bleeding decreased by 56.5% (95% CI, 41.9%-71.1%).[7] Mortality from NVUGIB is mostly due to complications of co-morbid illnesses. In a large observational study in the United Kingdom, mortality from NVUGIB in patients less than 60 years of age without concurrent illnesses was only 0.1%.[17] However, in a cohort of Chinese patients with endoscopically-confirmed NVUGIB, the mortality rate was 6.2%. All-cause mortality was significantly higher (79.7 %) than bleeding-related mortality (18.4 %). Common causes of mortality were multi-organ failure (23.9 %), pulmonary

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conditions (23.5 %) and terminal malignancy (33.7 %).[18]

In 2010, a collection of gastroenterologists and surgeons who are in active clinical practice and research in gastroenterology from 12 countries/regions, known as the Asia-Pacific working group of upper gastrointestinal bleeding (APWG-UGIB), published the Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding.[19] The guidelines, which included twelve (12) statements, was in pursuit of the spirit of the International Consensus Recommendations (ICON-UGIB), which encouraged regional specialty bodies to modify and create a region-specific set of guidelines to tailor-fit certain recommendations to the prevailing clinical practices and healthcare resources in different areas of the world.[20]

These current guidelines are a composite of 15 evidence-based recommendations directed towards a more uniformly comprehensive approach to the management of non-variceal upper gastrointestinal bleeding (NVUGIB), taking into consideration what can work best to a greater number of patients all over the country given the current realities of clinical practice, availability of expertise and appropriate equipment, hospital, and other economic challenges prevailing in the Philippines. By its very nature, these set of recommendations are deemed to increase the likelihood of achieving, but not ensuring definitively, desired treatment outcomes wherever they are applicable.

Methodology

To determine the applicability and feasibility of current guidelines to the prevailing healthcare situation in the Philippines, a review of the consensus statements and listed references of the ICON-UGIB 2010 and the APWG-UGIB 2011 was undertaken by a core working group composed of seven members (Sollano J, Daez ML, Dee G, Labio E, Lontok M, Santos D, and Romero R). The members were chosen for their academic affiliations, expertise in evidence-based medicine, active clinical practice, and research in gastroenterology. Literature searches were performed in Medline, Embase, the Cochrane Central Register of Controlled Trials and ISI Web of Knowledge, including manual searches in bibliographies of key articles, proceedings of abstracts of major gastroenterology and endoscopy meetings held in the past five years (Asian Pacific Digestive Week (APDW), Digestive Disease Week (DDW), and United European Gastroenterology Week (UEGW) and articles published in the Philippine Journal of Internal Medicine and Philippine Journal of Gastroenterology. Local data gathering was also performed through a review of the scientific papers submitted by fellows-in-training from different accredited training institutions of the Philippine Society of Gastroenterology (PSG). In addition, an electronic data collection form was circulated to 15 training institutions and another 12 urban centers with gastroenterology and endoscopy facilities from all over the country to generate up-to-date information on demographics, etiology, management, and outcomes of consecutive NVUGIB patients seen over the last 12 months.

A Knowledge Attitudes and Practices (KAP) survey was also accomplished by the Training Program Directors, Chiefs of Section and Training Officers of each participating institution. A pre-consensus development conference was held where the results of the surveys and reviews were presented and discussed. Important issues were identified and forwarded to the core working group for further deliberations. Following the modified Delphi process, 17 recommendations were proposed by the core working group for electronic voting by email. Voting for every statement was done as follows; (1) Accept completely; (2) Accept with some reservation; (3) Accept with major reservation; (4) Reject with reservation; (5) Reject completely. Additional comments were encouraged for each statement and revisions were made accordingly during subsequent deliberations of the core working group.

After the electronic voting, a consensus development conference was held in January 2012 participated by all training program directors, chiefs of section, PSG officers, and committee chairs and members of the core working group. Each participant was assigned to present and defend a statement/recommendation. During the conference, the presenters were required to evaluate newer/later publications which were not included and considered in the APWG-UGIB, taking special care to include publications from Asia. Liberal discussion and debate was encouraged during the conference and subsequent voting on every statement was conducted anonymously using wireless keypads. If the pre-determined agreement of 85% was not achieved, the statement/s is/are rejected. The level of evidence and the strength for each recommendation were rated by the participants using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process, as follows: a) High — further research is very unlikely to change our confidence in the estimate of effect; b) Moderate — further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; c) Low — further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; d) Very low — any estimate of effect is uncertain. The strength of recommendation was classified as follows; a) strong b) conditional. The participants were constantly reminded that care is needed so as to recognize that `quality of evidence` is not necessarily synonymous with `strength of recommendation,` and vice versa; and that their informed judgment is necessary.[21]

An unrestricted, arms-length grant from AstraZeneca and a seed fund from PSG made possible the preparation and completion of this document. During the entire duration of the consensus process, as well as in the writing of the manuscript, no interference or representations by any third party were allowed by the consensus development group.

Consensus Statements

Recommendation 1:

Utilization of risk scoring systems is recommended to stratify patients with NVUGIB who may require endoscopic intervention and/or are at risk for re-bleeding or mortality.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

There are many scoring systems which are utilized to stratify the risks associated with non-variceal upper GI bleeding, e.g., Cedars-Sinai, Baylor, the Italian PNED, etc. However, the Rockall and the Blatchford scoring systems are used widely and have been validated in many centers worldwide. Combining a number of clinical and laboratory data, as well as endoscopic stigmata of recent hemorrhage, the Rockall Score can predict increased risks of rebleeding and mortality in patients with NVUGIB.[22]

On the other hand, the Glasgow Blatchford Score (GBS) utilizes largely clinical and laboratory data which can be determined early and easily even in the emergency room. It is able to discriminate well between patients with NVUGIB who needs additional clinical intervention from those who do not.[23] A retrospective study showed that a high-risk Blatchford score has a higher sensitivity than the clinical and post-endoscopic Rockall score in predicting the need for clinical intervention.[24] In a large RCT among Chinese patients, the Blatchford score was found to be more useful in identifying the low-risk patients who may not need therapeutic endoscopic procedures, and are thus suitable for outpatient management. The pre-endoscopic Rockall score was unable to predict this need.[25] The Progetto Nazionale Emorragia Digestiva (PNED) score was recently validated in an independent population of non-variceal bleeders and was shown to have a high discriminant capability and was significantly superior to the Rockall score in predicting the risk of death (AUC 0.81 (0.72 – 0.90) vs. 0.66 (0.60 – 0.72), $p < 0.000$). The positive likelihood ratio for mortality for patients with a PNED risk score > 8 was 16.05.[26]

A study of 2,832 patients showed that the adoption of the Rockall scoring system in several gastroenterology units in Italy resulted in shorter hospital stays, lower rebleeding rates, and a decline of mortality in NVUGIB patients.[27] A recent Danish study prospectively compared the age-extended GBS (EGBS), the Rockall score, the Baylor bleeding score, and the Cedars-Sinai Medical Center predictive index and concluded that the Glasgow Blatchford Score can accurately identify the patients with UGI hemorrhage who will most likely need a hospital-based intervention versus those best suited for outpatient care.[28] Despite the advantages and benefits proven by many trials, our national NVUGIB survey revealed that risk stratification among NVUGIB patients who present in the emergency room is not practiced in most centers in the Philippines. Clearly, a local validation study will be most helpful in determining the overall applicability of these scoring systems among Filipino patients. However, in the context of the evidence gathered thus far, the Consensus Working Party strongly recommends that henceforth, this strategy should be a part of the initial assessment of all NVUGIB patients in the country.

Recommendation 2:

Acute blood loss should be replaced with packed red blood cell transfusions to achieve a hemoglobin level of at least 10 g/dL.

Consensus Vote: 89.5%
GRADE Quality of Evidence: Low
Strength of Recommendation – Conditional

In order to maintain adequate tissue perfusion and oxygenation, restoration of blood volume and hemoglobin levels should be pursued aggressively during resuscitation of patients with acute blood loss related to NVUGIB. In a prospective cohort study of patients with GI bleeding, a hemoglobin level <8.2 g/dl was a significant risk factor for myocardial necrosis.[29] It must be emphasized, however, that the threshold for transfusion for each patient should be based on his/her underlying condition, hemodynamic status, and markers of tissue hypoxia in acute situations as there are also risks associated with blood transfusion.[20] A recent meta-analysis revealed blood transfusion increases mortality rates, as well as risks for nosocomial infection, multi-organ dysfunction, and acute respiratory distress syndromes in a heterogeneous group of critically ill patients in the intensive care units, orthopedic and trauma centers, etc.[30]

The ICON-UGIB recommends that transfusion should be started at hemoglobin 7 g/dL or less while the Asian Pacific Consensus Guidelines did not specify a certain threshold. In the absence of coronary artery disease, the Working Party agrees with international guidelines recommending the initiation of red blood cell transfusion when the hemoglobin level is 7 g/dL, although it may be started earlier in the elderly patients with NVUGIB.[31]

Furthermore, a cohort study of patients with acute upper GI bleeding demonstrated that endoscopy may be performed safely in patients whose hematocrit level is <30 cv% compared to those with hematocrit levels above 30 cv%. There was also no difference in mortality in both groups.[32] On the other hand, a study on euvolemic but critically ill patients showed that 30-day mortality was similar for patients with hemoglobin between 7-9 g/dL, or those with hemoglobin of 10-12 g/dl.[33] Blood, blood products, and volunteer blood donors are difficult to come by in many centers in the country; thus, the objective of this recommendation is to guide clinicians on the appropriate hemoglobin level considered optimum during the resuscitation and blood replacement of patients with acute blood loss due to upper GI hemorrhage, as well as to rationalize the utilization of a precious yet scarce commodity in the healthcare delivery system of the country.

Recommendation 3:

The use of proton-pump inhibitors prior to endoscopy may downstage the severity of the endoscopic lesion but should not delay endoscopy.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation — Strong

For the ICON-UGIB, a meta-analysis of six RCTs and an abstract[34,35,36] showed that pre-endoscopy administration of PPIs downstages effectively the bleeding lesion, resulting in a reduction of the proportion of patients exhibiting high-risk stigmata of recent hemorrhage at the time of endoscopy (OR 0.67, 95% CI 0.54-0.84), as well as the need for endoscopic intervention (OR 0.68, 95% CI 0.50-0.93).

The cost-effectiveness of this approach may be optimized if it is performed in the subgroup of patients with a greater likelihood of having a high-risk lesion, e.g., those who present with hematemesis of bright red blood.[20] Meanwhile, the Asia-Pacific consensus recognized the fact that patients' access to endoscopic facilities with available expert staff and personnel able to handle adequately all forms of NVUGIB vary widely across the region. Pre-endoscopy PPI infusion may be a good strategy to follow in locales where endoscopy is not available within 24 hours because it will allow time for adequate resuscitation and preparations for a transfer to a better equipped center. These conditions are prevalent in the Philippines, thus this Working Party recommends that after ascertaining that the bleed is compatible with a non-variceal etiology, prompt administration of PPIs must commence upon admission. Clearly, a proper and thorough bedside evaluation must be performed and the diagnosis of a NVUGIB is reasonably certain before PPI administration is started. The unwarranted use of PPIs on all patients who present with upper GI hemorrhage should be avoided at all times and this current management guideline emphasizes it strongly.

In Asia, the dose and route of the PPIs have been studied extensively; the current practice is to give an 80 mg IV bolus followed by an infusion of 8 mg/hr.[35] High dose PPI given pre-emptively decreases gastric pH, ensures stability of the fibrin clot, and aids in initial hemostasis prior to endoscopy. It must be emphasized though that such medical intervention should not, in any way, delay endoscopy.

Lower doses of IV PPI may have practical applicability in rural areas or in poor urban centers in the country but there are no adequately-powered studies to support this strategy. A Cochrane meta-analysis of randomized trials of patients with UGIB who did not consistently receive endoscopic hemostatic therapy revealed that PPI therapy was associated with reduced rebleeding and surgery, but not mortality.[37] This suggests that if endoscopy will be delayed or cannot be performed, PPI therapy may improve clinical outcomes.[38]

Recommendation 4:

Utilization of risk scoring systems is recommended to stratify patients with NVUGIB who may require endoscopic intervention and/or are at risk for re-bleeding or mortality.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

Earlier studies with H2-receptor antagonist (H2RA) use in NVUGIB showed conflicting results, and benefits in reducing rebleeding rates were only demonstrated in bleeding gastric ulcers but not in duodenal ulcers.[39,40,41,43,44] Comparative trials of H2RAs versus PPIs demonstrated the superiority of PPIs in decreasing risks of rebleeding, as well as reducing transfusion requirements and hospital stay. There was no difference in the need for surgery or mortality rates.[44,45,46,47] Given that during the initial resuscitation of bleeding patients, clinicians are unaware of the nature and etiology of the bleed, it is deemed inappropriate to start administration of an agent which may not be effective for all the common causes of NVUGIB. Tachyphylaxis is also a phenomenon which is observed during H2RA use. Earlier studies have shown that even when administered intravenously in high doses, H2RAs cannot maintain intragastric pH above 6 beyond 24 hours because of the rapid development of tolerance.[48,49] Thus, it is not recommended as a first-line treatment option in acute NVUGIB.

Studies with tranexamic acid were either underpowered or flawed and there have been no recent trials to show benefits in NVUGIB.[50,51] A meta-analysis of 14 studies performed in the 1990s using

intravenous somatostatin or octreotide, its longer-acting analogue, demonstrated advantage of somatostatin in reducing the rebleeding rates and need for surgery.[52] A Korean retrospective study revealed that there was no difference in rebleeding rates and in downgrading stigmata of recent haemorrhage among patients given somatostatin versus high-dose PPI infusion.[53] Concerns about known cardiovascular side-effects related to vasoactive agents, e.g., somatostatin and octreotide should be considered when using these agents, especially in elderly patients with known cardiovascular risks. Moreover, the ease of use and the general accessibility of cheaper IV PPIs are important considerations in the clinical decision making process of choosing the appropriate first-line agent to administer during hospital admissions of patients with NVUGIB, be it in a well-equipped urban center or in a resource-scarce rural setting. Thus, at the current level of evidence, the routine use of H2-blockers, tranexamic acid, somatostatin, and octreotide is not recommended.

Recommendation 5:

In high-risk patients with NVUGIB, endoscopy should be performed within 24 hours of presentation.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

Recent guidelines state that early endoscopy, i.e., within 24 hours of presentation, is recommended for most patients with acute upper gastrointestinal bleeding. A meta-analysis of three trials done by the ICON-UGIB Conference Group has shown no significant difference in outcomes of reduction in rebleeding, need for surgery and mortality rates between urgent endoscopy (<12 hours) and early endoscopy (>12 - 24 hours).[20,54]

Generally, early endoscopy, and not emergency endoscopy, is preferred. During the early hours of hospitalization, volume replacement and stabilization of the patients are the most important objectives of treatment. Furthermore, the performance of endoscopy and the related endotherapeutic procedures, when needed, is facilitated by the availability of the entire support staff during normal working hours.

A recent prospective study performed in Singapore showed that in high-risk patients with Glasgow Blatchford Score of 12 or more, the performance of endoscopy within 13 hours of presentation was associated with lower all-cause in-hospital mortality.[55] A prospective validation study of pre-endoscopic risk stratification scoring systems also demonstrated that the Glasgow Blatchford score of 0 at presentation can discriminate the low-risk patients who may not require immediate endoscopy for endoscopic hemostasis of their NVUGIB lesions.[25] During the discussions, it was agreed that urgent endoscopy may be performed amongst haemodynamically unstable patients or in those with massive hematemesis, once stabilized and resuscitated adequately. On the other hand, endoscopy may be postponed in those with associated critical and/or severe cardiopulmonary conditions.

Recommendation 6:

Endoscopic hemostasis using epinephrine injection should be administered only in combination with other endotherapeutic modalities.

Consensus Vote: 100%
GRADE Quality of Evidence: High
Strength of Recommendation – Strong

Injection hemostasis using 1:10,000 epinephrine is superior to medical therapy in patients with NVUGIB. However, several meta-analyses have demonstrated that the combination of epinephrine injection with another method, i.e., alcohol, thrombin, or fibrin glue, significantly reduces rebleeding rates, need for surgery, as well as mortality rates in patients with high-risk stigmata of recent hemorrhage.[56,57,58] Compared with epinephrine alone, a recent meta-analysis demonstrated that further bleeding was reduced significantly with epinephrine injection followed by another modality (RR, 0.34 (95% CI, 0.23–0.50); NNT, 5(95% CI, 5–7)).[59] In a nationwide survey, majority of endoscopy centers in the country were found to be equipped only to administer epinephrine injection monotherapy. In the light of this evidence, it is strongly recommended that a second endotherapeutic modality, if not the complete set of endoscopic hemostatic gadgetry, be made available to endoscopists in these centers so that a combined approach to endoscopic hemostasis is administered to patients with NVUGIB.

Recommendation 7:

Where expertise and equipment are available, endoscopic hemostasis with sclerosant injection, thermocoagulation and hemoclip application may be used alone.

Consensus Vote: 100%
GRADE Quality of Evidence: High
Strength of Recommendation – Strong

Several meta-analyses have shown that compared to epinephrine alone or to pharmacotherapy alone, monotherapy with sclerosant injection, thermocoagulation, and hemoclip application are far more effective modalities for endoscopic hemostasis.[58,59,60] Monotherapy with thermal contact reduces rebleeding rates and need for urgent intervention when compared to sclerosant injection (further bleed OR, % CI 0.69 (0.47–1.01); urgent intervention OR, % CI 0.52 (0.31–0.88) or sclerosant + epinephrine (further bleed OR, % CI 0.72 (0.51–1.02); urgent intervention OR, % CI 0.60 (0.37–0.97). Mortality rates and need for surgery were not significantly

different.[59] A recent randomized controlled trial (RCT) from Japan revealed that soft coagulation is as effective as hemoclip application for bleeding gastric ulcers.[61] Meta-analysis of two Asian studies comparing hemoclips with epinephrine,[62] and comparing epinephrine with hemoclip followed by epinephrine[63] revealed that further bleeding and need for surgery were decreased with hemoclips alone (further bleed OR, % CI 0.22 (0.09–0.55); need for surgery OR, % CI 0.22 (0.06–0.83), or with hemoclip application followed by epinephrine (i.e., further bleed (OR % CI 0.92 (0.48–1.77). Mortality rates were not significantly different. Fibrin glue and thrombin monotherapy are also effective therapies; however, because they are not readily available in the country, these endotherapeutic options were not considered by the Working Party. Thus, it is highly recommended that any one of the following instruments — heater probe, BICAP, or hemoclip applicator — should be available in all endoscopy units in the country.

Recommendation 8:

After a successful endoscopic hemostasis, high-dose PPI infusion may reduce rebleeding and need for surgery in high-risk patients with NVUGIB.

Consensus Vote: 100%
GRADE Quality of Evidence: High
Strength of Recommendation – Strong

International and regional clinical practice guidelines recommend that high-dose PPI infusion should be administered after successful endoscopic hemostasis. An IV bolus followed by high-dose PPI drip reduces rebleeding, need for repeat endoscopic intervention, and surgery and blood transfusion requirement. Two Cochrane meta-analyses have demonstrated further that mortality rates are also reduced by this strategy.[64,65] An international randomized controlled trial designed to determine whether intravenous esomeprazole prevents recurrent peptic ulcer bleeding better than placebo in a multi-ethnic patient sample revealed similar relative reductions in recurrent bleeding at 72 hours, although the rebleeding rate was lower in White patients, i.e., 5.5% for esomeprazole versus 10.8% for placebo, compared to the Asian patients, i.e., 3.7% for esomeprazole vs. 7.4% for placebo.[66] An Asian study has shown that this strategy is also a cost-effective approach to NVUGIB.[67]

During discussions in the AsiaPacific Consensus, it was concluded that there was insufficient data to justify the use of low-dose IV PPIs. A recent single-center RCT from Singapore showed that intravenous standard-dose omeprazole (40 mg daily for three days) was inferior to high-dose omeprazole in preventing rebleeding after endoscopic hemostasis for peptic ulcer bleeding.[68]

On the other hand, it must be noted that in Asia oral PPIs have been administered with considerable success as adjunct to endoscopic therapy for NVUGIB.[69,70] This observation has been noted by several meta-analyses[64,65] and thus, the ICON-UGIB, as well as, the Philippine Working Party also recommends that high-dose oral PPIs, i.e., equivalent to four times the standard daily oral dose, may be considered as an adjuvant treatment after endotherapy has achieved a secure hemostasis in patients with NVUGIB.

Recommendation 9:

Each institution should establish treatment protocols and provide adequately trained staff to promote a multidisciplinary approach to UGIB management.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

In the Philippines or in many other regions of the world, there are wide variations in the resources available in many centers, including availability of an endoscopy service, an appropriate set of endoscopic gadgets needed for hemostasis, expert endoscopist/s and trained support staff, etc. In addition, endoscopy services may be accessed only in urban centers. Patients who are able to reach or force their way into these centers may be in more serious condition; thus, the seamless performance of endotherapeutic and/or surgical hemostatic procedures should be always the norm. In 2003, ICON-UGIB recognized the uneven conditions of healthcare in many parts of the world and addressed this issue by re-emphasizing that centers should be encouraged to "develop institution-specific protocols for multidisciplinary management; (and to) include access to an endoscopist trained in endoscopic hemostasis and have available on an urgent basis support staff trained to assist in endoscopy".[71,72,73,74,75] Several studies have demonstrated that the presence of a "bleeding team" reduces mortality and hospital costs. This team usually consists of the following: gastroenterologist/endoscopist, surgeon, radiologist, endoscopy nurse, hematologist, and medical technologist. Other support systems, e.g., blood bank, surgical theaters, weekend endoscopy service, etc. should operate in close coordination with the endoscopy unit in the management of a patient with NVUGIB. Not an uncommon scenario in the Philippines, delays in administering blood transfusion due to unavailability of blood products in poorly-managed blood banks should be addressed promptly and adequately by hospital authorities. The creation of an institution-specific multidisciplinary bleeding team is also highly recommended.

Recommendation 9a:

A surgical consultation should be made when initial endoscopic therapy fails.

Consensus Vote: 94.7%
GRADE Quality of Evidence: Low
Strength of Recommendation – Conditional

After an attempt at endoscopic hemostasis, up to 1.5% will continue to bleed while rebleeding is observed in 8.7% of Chinese patients.[76] In a North American cohort, continued bleeding or rebleeding occured in 14.1% of patients who received endoscopic therapy, and up to 6.5% of those who continued to bleed eventually needed surgery.[77] In the Asian study mentioned above, 27% who re-bled after endoscopic therapy had to undergo a rescue surgery to stop the bleed.[76] In the same trial, an endoscopic re-treatment was found suitable for smaller ulcers in patients with relatively stable hemodynamics because this strategy had a high rate of success and was associated with lesser complications, but not for large ulcers. Given the limited and widely disparate instrument and/or manpower resources available in many of the endoscopy centers of the country, the Working Party recommends that a referral for a surgical back-up may be necessary as early as after a failed first attempt at endoscopic hemostasis. A local multicenter prospective randomized trial is recommended to test the validity of this hypothesis.

Recommendation 9b:

When available, angiographic embolization is an alternative to surgery for patients with failed endoscopic hemostatic therapy.

Consensus Vote: 94.7%
GRADE Quality of Evidence: Low
Strength of Recommendation – Strong

The first report of selective arterial embolization of the gastroepiploic artery for the control of acute gastric bleeding was made in 1972. Embolization of a bleeding UGI vessel may be done using gelatin sponge, steel coil, polyvinyl alcohol, or N-butyl-cyanoacrylate.[78] Vast improvements in catheter-based therapy have been achieved since and, currently, angiographic embolization of NVUGIB may be recommended to patients who have a massive bleed but have failed endoscopic hemostasis or in those who have undergone surgery and suffers a re-bleed. Several retrospective trials have shown that there may be no significant differences in the rates of rebleeding, surgery or mortality between percutaneous angiographic embolization treatment and surgery in patients who experience rebleeding. It is also an effective procedure for endotherapy failures.[79,80,81] A review emphasized that there can be no absolute contraindications because angiography and embolization may be needed as a lifesaving procedure.[82] When rebleeding occurs, a repeat attempt at endoscopic hemostasis may be attempted[19,20,71] or a surgical referral must be made as has been recommended by this guideline. However, wherever expertise and machines are available and the patients have serious contraindications to surgery, the percutaneous angiographic route of hemostasis may be pursued in this special subset of patients.

Recommendation 10:

In all patients with ulcer bleeding, testing and eradication of *H. pylori* infection should be performed, and eradication of infection confirmed.

Consensus Vote: 100%
GRADE Quality of Evidence: High
Strength of Recommendation – Strong

It has been observed that H. pylori infected patients with NVUGIB have better outcomes when given PPI infusion. In the international peptic ulcer bleeding study the rebleeding rates were lower in the patients with H. pylori infection than in those who are not infected, 3.7% versus 9.8%, respectively.[66] This favorable outcome in patients who have NVUGIB can be attributed to a more profound acid suppression achieved by PPIs in patients who have pre-existent low gastric acid outputs resulting from there H. pylori infection.

Clinical practice guidelines recommend testing for and treating H. pylori in patients with NVUGIB. Gisbert et al. in a meta-analysis has shown that H. pylori eradication is significantly better in preventing a recurrent bleeding from peptic ulcers compared to PPI therapy alone, i.e., OR, % CI 0.17, 95% CI 0.10-0.32.[83] A systematic review and meta-analysis of the diagnostic accuracy of different tests for H. pylori detection in patients with NVUGIB revealed that biopsy-based methods, such as rapid urease test, histology, and culture, have a low sensitivity, but a high specificity when performed during the UGIB event. On the other hand, the accuracy of 13Carbon urea breath testing remains very high in these patients while the stool antigen test is less accurate. Serology seems not to be influenced by bleeding but may not be recommended as the diagnostic test of choice in this setting.[84] A more recent systematic review of 24 studies showed that in the setting of acute UGIB, between 25% to 55% of H. pylori–infected patients may have false-negative results when using any of the available H. pylori tests.[85] Thus, it is advised that a careful interpretation of H. pylori test results must be done in these situations and re-testing may have to be performed during follow-up in the appropriate patient setting.20 As a standard of care, confirmation of successful H.

pylori eradication should be pursued in all patients receiving eradication regimens.

Recommendation 11:

In patients with arthritis who have a history of ulcer bleeding, the use of a COX-2 selective NSAID plus a proton-pump inhibitor is associated with the highest reduction in risk for re-bleeding.
Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

In order to reduce ulcer complications, the Asian Pacific Working Party in 2010 recommended the use of COX-2 selective inhibitors alone or a combination of a non-selective NSAID plus a PPI in patients with arthritis who had prior ulcer bleeding. An RCT from Hong Kong involving 242 H. pylori negative patients with prior ulcer complications due to NSAIDs showed that the use of naproxen 750 mg plus PPI co-therapy was as effective as the use of COX-2 inhibitors (COXIBs) alone in the prevention of recurrence of ulcer complications. However, these strategies did not completely eliminate these risks, noted in 6.3% of the PPI co-therapy group and 3.7% in the COXIB group.[86] An earlier study showed similarly a significant but not absolute reduction in ulcer complications in those who are treated with diclofenac Na plus a PPI or with COX-2 inhibitors alone, i.e., 6.4% and 4.9%, respectively.[87] A population-based study showed that the use of commonly accepted gastroprotective strategies reduce the risk of upper GI tract complications among NSAID users, and the combination of COX-2 inhibitors with PPIs achieved the greatest reduction in risks.[88] A multicenter Asian RCT involving H. pylori-negative patients with arthritis and had a history of ulcer bleeding related to intake of nonselective NSAIDs showed that the combination of COX-2 inhibitors and a PPI was more effective than COX-2 inhibitors alone in the prevention of ulcer rebleeding in patients at high risk.[89] Current evidence therefore suggests that the combination of COX-2 inhibitors with a PPI is associated with the highest reduction in the risk for a recurrent ulcer complication among high-risk patients requiring NSAID therapy.

Recommendation 12:

Among aspirin users with high cardiothrombotic risks who develop ulcer bleeding, prolonged discontinuation of aspirin is associated with increased mortality.
Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

Aspirin is effective in the prevention of cardiac and cerebrovascular events among patients at high risk. The dose range recommended for primary and secondary prevention of coronary artery disease (including those from Food and Drug Administration-approved labeling) is 75–325 mg daily.[90] Among high-risk patients, aspirin is associated with an overall 35% odds reduction of non-fatal myocardial infarction and 31% odds reduction of non-fatal stroke.[91] However, even low-dose aspirin (75-325 mg/day) increases the risk of any major bleeding by approximately 70%. In a meta-analysis of placebo-controlled trials on vascular protection, the relative risk of major gastrointestinal bleeding with low-dose aspirin was 2.07 (95% CI: 1.61–2.66).[92]

Discontinuation of aspirin and/or antiplatelet therapy is standard clinical practice when UGI bleeding occurs. However, a recent Asian trial showed that patients who withdrew aspirin early and discontinued aspirin for eight weeks after they developed UGI hemorrhage had a higher all-cause mortality rate compared to those who had early resumption of aspirin administration, 12.9% versus 1.3%; difference, 11.6 percentage points (CI, 3.7 to 19.5 percentage points). In contrast, patients who had early resumption of aspirin had lower mortality rates attributable to cardiovascular, cerebrovascular, or gastrointestinal complications, 1.3% versus 10.3%; difference, nine percentage points (CI, 1.7 to 16.3 percentage points).

Meanwhile, withdrawing aspirin at the onset of UGI bleeding resulted in lower 30-day rebleeding rates (5.4% vs 10.3%; difference, 4.9 percentage points (95% CI, 3.6 to 13.4 percentage points)).[93]

Thus, in the management of patients who have bleeding ulcers with high-risk stigmata of recent hemorrhage, it is recommended that after a secure endoscopic hemostasis has been attained, resume the aspirin three to five days after the last dosing. In patients with low-risk stigmata antiplatelet, therapy may be resumed immediately after successful endoscopic hemostasis.[94] Currently, there are no sufficiently-powered studies that demonstrate when to resume safely clopidogrel or dual antiplatelet therapy in patients with high cardiothrombotic risks who develop a NVUGIB.

Recommendation 13:

Clopidogrel alone is not an alternative to aspirin plus PPI in patients with increased risk of ulcer bleeding; however, clopidogrel plus PPI may reduce the risk.
Consensus Vote: 94.7%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

It is complacent to presume that clopidogrel is a safer antiplatelet treatment alternative. In 2008, expert gastroenterologists and cardiologists advised that

clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding. Hemorrhage may be due to lesions like erosive esophagitis,[95] gastroduodenal erosions, as well as peptic ulcerations produced by H. pylori infection, aspirin and other NSAIDs.[96] Several clinical characteristics increase the risks of GI bleeding including advanced age, concurrent use of anticoagulants, steroids, or NSAIDs including aspirin, and Helicobacter pylori infection. The risk of GI bleeding increases as the number of risk factors increases, and patients with prior upper GI bleeding from peptic ulcers are at highest risk for recurrent bleeding while on antiplatelet therapy.[97,98]

Two Asian RCTs which had at least 12 months of follow-up[99,100] were included in the meta-analysis done for the ICON-UGIB. This meta-analysis showed that ASA plus a PPI significantly reduced rebleeding compared to clopidogrel monotherapy, i.e., rebleeding OR 0.06 (95% CI 0.01-0.32). There was no difference in mortality, OR 0.63 (95% CI 0.24-1.64), as well as in the development or relapse of cardiovascular or cerebrovascular events. Clopidogrel increases the risk of recurrent bleeding more than 10 times, but not the incidence of lower GI bleeding.[101] If clopidogrel is the chosen antiplatelet agent, co-administration with a PPI is recommended.[102]

Recommendation 14:

Among patients receiving dual anti-platelet therapy, prophylactic use of proton-pump inhibitors reduces the risk of upper GI bleeding.

Consensus Vote: 100%
GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong

In patients undergoing percutaneous coronary intervention, the continuation of clopidogrel and aspirin therapy for one year leads to a significant reduction in irreversible atherothrombotic events.[103] As shown in an earlier study, however, co-administration of these two antiplatelet agents increases the risk of a major UGI bleed from 0.7% to 1.3%.[105] As a strategy to reduce the GI risks of combination antiplatelet and NSAID use, a panel of experts in 2008 recommended the use of a proton pump inhibitor co-medication.[98] However, numerous reports which followed after publication of these recommendations suggested that the concomitant use of clopidogrel and a PPI reduces the antiplatelet effects of clopidogrel. It must be noted that majority of these trials were largely retrospective, cohort, or case-control studies.

A recent Asian double-blind, randomized control trial showed that esomeprazole and famotidine do not reduce the platelet inhibition of clopidogrel.[105] The COGENT randomized control trial which was published recently tried to demonstrate that concomitant intake of clopidogrel and omeprazole does not have cardiovascular interactions which may diminish the clinical efficacy of clopidogrel. In addition, prophylactic PPI co-therapy reduced the rate of upper gastrointestinal bleeding in patients treated with aspirin and clopidogrel. However, the trial is underpowered as it was terminated prematurely before recruiting the estimated sample size. Given that the confidence interval around the hazard ratio for cardiovascular events is wide, the observed absence of interaction between clopidogrel and omeprazole may not be definitive as yet.[102] Despite these reservations, the ACCF/ACG/AHA expert consensus group, as well as the Asia-Pacific Working Party recognized the appropriateness of prophylactic PPI use in patients with multiple risk factors for GI bleeding who require antiplatelet therapy. They recommended further that clinical decisions regarding concomitant use of PPIs and thienopyridines must balance the overall risks and benefits associated with this intervention, with special considerations on both CV and GI complications.[106] This Working Party recommends that a PPI be co-administered for patients receiving dual antiplatelet therapy largely because it lowers the risk of upper GI bleeding in patients at risk. There are suggestions that taking the PPI and clopidogrel several hours apart (e.g., 12 hours) may minimize their interaction given that the half-lives of both drugs are short, i.e., less than two hours. A crossover trial involving 72 patients did not seem to support this concept.[107] Thus, unless there are bigger trials which clarify this hypothesis, it may not be beneficial to recommend changes in the usual dosing schedule of these drugs.

Recommendation 15:

Proton-pump inhibitors are superior to H2-blockers as co-medication to prevent ulcer bleeding in patients receiving anti-platelet therapy.

Consensus Vote: 100%
GRADE Quality of Evidence: High
Strength of Recommendation – Strong

Compared to placebo, a Cochrane systematic review has shown that H2-receptor antagonists decrease better the risks for NSAID-induced gastric and duodenal ulcers.108 An RCT has also demonstrated that H2RAs are effective in reducing the risk for ulcers related to low-dose aspirin given as antiplatelet treatment.95 Several studies, however, have shown that PPIs are more superior than H2RAs in preventing peptic ulcers,[109,110,111] as well as in preventing UGI bleeding associated with aspirin or thienopyridines.[99,100,112]

Overall, current data suggest that H2RAs are inferior to PPIs in preventing peptic ulcers related to NSAID, aspirin, and clopidogrel treatment, including a significant disadvantage in the prevention of recurrent hemorrhage in high-risk patients. As mentioned earlier

in this document, another major concern regarding the long-term efficacy of H2RAs in patients who will be receiving antiplatelet therapy for a considerable length of time is the phenomenon of tachyphylaxis observed commonly with prolonged H2-blocker treatment.[48] Thus, the use of PPIs as co-medication is preferred in patients receiving dual anti-platelet therapy.

Dissemination and Update of Recommendations

These recommendations shall be published in a peer-reviewed scientific journal of nationwide distribution. To ensure further the maximum reach of this clinical practice guideline, it shall be presented in national, regional and specialty conferences throughout the country. In partnership with third parties, we shall also take every opportunity to speak about the recommendations in all fora covering NVUGIB. Reprints of these guidelines shall be mailed to every member of the Philippine Society of Gastroenterology and of the Philippine College of Physicians. All Sections of Gastroenterology and Endoscopy Units in all hospitals in the Philippines shall be encouraged strongly to implement the guidelines wherever they are applicable. Inasmuch as all the Training Program Directors were part of the guideline development process, all centers with gastroenterology training programs shall implement these recommendations in their respective institutions. Updates of these recommendations shall be made regularly and whenever deemed necessary depending upon the quality and weight of accumulated new scientific publications regarding the management of NVUGIB.

Acknowledgement

For sharing NVUGIB data from their respective centers and participating in the pre-consensus conference deliberations official recognition and acknowledgments are extended to Agas F, Alli M, Balay A, Bascug M, Cloa M, Encarnacion D, Fonbuena G, Galang A, Gamutan T, Gonzales E, Hababag W, Macatula T, Mercado R, Otero G, Soriano J, Tam R, Ugpo J, and Yap R.

Special acknowledgments to Romeo Romano, MD for developing the electronic NVUGIB national database and special assistance extended to the Core Working Party during the entire process of data gathering, analysis, and interpretation.

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