Expert Opinion by Brian Liem, DO and Michael Sprang, MD
Intermittent vs Continuous Proton Pump Inhibitor Therapy for High-Risk Bleeding Ulcers

In the cost-conscious reality we are in, striving to decrease health care costs is important; from decreasing length of stays to the effective ordering of medications and diagnostic tests, we are constantly seeking algorithms to effectively and safely take care of patients while reducing costs. In the study by Sachar, et al., we look at the acute management of high-risk bleeding ulcers and the use of proton pump inhibitors.

The current guidelines, as noted in your clinical scenario, were set forth by the American College of Gastroenterology (ACG) in 2012, stating the use of IV PPI, first with a bolus, and then followed by a continuous infusion for 72 hours, following endoscopic hemostasis. The basis of these guidelines was not to promote the healing of the gastric ulcer, but to increase intragastric pH to greater than 6 to promote clot formation at the site of injury immediately following intervention. Studies of this phenomenon go back to the 1970s, showing that at a pH of less than 6.4 intrinsic and extrinsic coagulation, along with polymerization of fibrinogen and the availability of platelet phospholipids were affected. Furthermore, at a pH of 5.4, in vitro, platelet aggregation and plasma coagulation did not occur. It was also noted pepsin increased platelet disaggregation. Since gastric acid not only affects clot formation but the activation of pepsin from pepsinogen, the importance of reducing gastric acid is key in the control of a GI hemorrhage.

In our practice, the application of IV PPI via bolus and continuous infusion versus intermittent dosing is not as clear cut despite years of research and data. The current guidelines for management of high-risk bleeding ulcers were from 2012, and the Sachar, et al. article was from 2014, stating that "current national and international guidelines should be revised to incorporate this new information and recommend intermittent PPI therapy," however, no revision has occurred. This shows that there is still somewhat of a lack of consensus in the GI community. It is interesting to note that Loren Laine, MD, a very well-known and respected gastroenterologist in the GI community, and who was the main author of the current ACG guidelines from 2012, was also the senior author on the paper recommending changes to these very guidelines.

To make significant changes in clinical practice and to practice evidence based medicine, it is vital to understand the data used to establish the standard of care. There are limitations to any study, a fact that has prompted this conference series. Of note, there is a large heterogeneity in endoscopic therapy and PPI dosing used amongst the sources. There were studies that used monotherapy for hemostasis which is not standard of care. The study also reinforces that we do not know the ideal dose and cumulative dose needed to provide effective hemostasis. Though the use of higher doses will lead to more persistent elevated intragastric pH, is there a dose that leads to a plateau not only in the intragastric pH and the length of time it is elevated, but in the formation and persistence of the clot? It is easy to err and give higher doses of a PPI to reduce the intragastric pH, but it is not understood at which point we plateau. It also appears to be unclear if there is any benefit to administering an initial high dose bolus prior to intermittent or continuous dosing therapy.

When comparing the relative risks amongst the studies between continuous vs intermittent dosing used in the meta-analysis, it is hard to determine if the relative risk is affected based on PPI used, dose, cumulative dose, route, stigmata of hemorrhage, or endoscopic therapy. However, from an efficacy and safety profile, it is important to note that there is non-inferiority towards the use of intermittent dosing, which is -2.6% (well below the inferiority margin of 3%). It is our belief that this is of key importance, and
therefore the use of either practice is acceptable. Though the guidelines from 2012 support the use of continuous infusion, newer studies have shown these may need to be reassessed and likely rewritten. Importantly, given the shortages and cost concerns of IV PPIs, the use of intermittent dosing will not only be cost saving (and time saving) but will not result in worsening morbidity and mortality to the patient. It also must be stressed that more studies looking at the dose necessary to achieve sustained elevated intragastric pH are needed to understanding the management of high-risk bleeding ulcers.

Finally, it is important to stress that the treatment of high-risk bleeding ulcers is not just with PPI therapy, but is coupled with timely endoscopic therapy with effective dual therapies (epinephrine and bipolar/heater probe or hemoclips) and adequate resuscitation. In cases of hemodynamic instability, it is vital the patient undergo hemodynamic stabilization. Amongst the gastroenterologists at Loyola, we support the use of intermittent PPI dosing, with pantoprazole 40 mg (or other PPI) IV, every 12 hours. Clinical judgment should be used in cases of recurrent hemodynamic instability and/or recurrent bleeding ulcer, where it would not be unreasonable to consider a continuous infusion.