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PPIs for the Management of Upper GI Bleed

Introduction

1. Upper GI bleed (UGIB) is a common reason for ED visits with a major cause of morbidity, mortality and medical care costs.
2. Peptic ulcer accounts for at least 50% of UGIB cases.
3. Patients with UGIB usually present with hematemesis, melena and/or hematochezia.
4. Upon presentation, hemodynamic status should be evaluated and resuscitation provided if necessary. Resuscitation can include blood transfusion for target hemoglobin *of* ≥7 g/dl.
5. Patients can be risk stratified to low or high-risk using the Rockall score (range 0-7) and Blatchford score (range 0-23).
6. Proton pump inhibitors (PPIs) remain one of the mainstays of pharmacological therapy for the management of UGIB. It can be initiated if endoscopy cannot be performed, will be delayed for >24 after presentation or following endoscopy.

	Pantoprazole	Esomeprazole	Omeprazole
Dose	**Initial** • Infusion: 80mg bolus then 8mg/hr continuous infusion for a total of 72hours • Intermittent: 80mg LD then 40mg IVP Q12H **Maintenance** • High-risk: 40mg PO BID for 14days, then 40mg PO once daily • Low-risk: 20mg PO once daily *Duration ranges from 4-12weeks	**Initial** • Infusion: 80mg bolus then 8mg/hr continuous infusion for a total of 72hours • Intermittent: 80mg LD then 40mg IVP Q12H **Maintenance** • High-risk: 40mg PO BID for 14days, then 40mg PO once daily • Low-risk: 20mg PO once daily *Duration ranges from 4-12weeks	**Initial** • IV Omeprazole not available in the U.S, give IV Pantoprazole or Esomeprazole **Maintenance** • High-risk: 40mg PO BID for 14days, then 40mg PO once daily • Low-risk: 20mg PO once daily *Duration ranges from 4-12weeks
Administration	IVP: Give over at least 2 minutes Continuous Infusion: 8mg/hr PO: Swallow whole without crushing or splitting 30-60minutes before food	IVP: Give over at least 3 minutes for dose <80 mg; Loading dose over 30 minutes Continuous Infusion: 8mg/hr PO: Capsule can be given orally or opened and mixed with 50mL water for NG administration	PO: Swallow whole without crushing or splitting 30-60minutes before food
PK/PD	**Onset:** IV 15 to 30 minutes, PO 2.5hrs **Absorption:** Rapid, well absorbed **Duration:** 24hours (IV and PO) **Distribution:** 98% albumin bound **Half-life elimination:** 1hr, 3.5-10hrs in CYP2C19 deficiency **Excretion:** Urine (71%), feces (18%)	**Distribution:** 97% protein bound **Metabolism:** Hepatic primarily via CYP2C19 **Half-life elimination:** 1 to 1.5hrs in adults **Excretion:** Urine (80%), 20% feces	**Onset:** PO 1hr **Absorption:** Rapid **Duration:** Up to 72hours **Distribution:** 95% albumin bound **Half-life elimination:** 30min – 1hr, 3 hrs in hepatic impairment **Excretion:** Urine (77%)
Adverse Effects	Headache, nausea, abdominal pain, diarrhea, vomiting	Headache, flatulence, nausea, dyspepsia, abdominal pain, diarrhea	Headache, abdominal pain, nausea, diarrhea, vomiting, flatulence
Drug Interactions & Warnings	Contraindicated with Atazanavir, Rilpivirine and their combinations	Contraindicated with Atazanavir, Rilpivirine and their combinations, CYP2C19 Inducers	Contraindicated with Atazanavir, Rilpivirine and their combinations, CYP2C19 Inducers
Compatibility	Compatible with D5W, NS or LR	Compatible with D5W, NS or LR	Not Applicable
Comments	PPIs may increase the risk of *Clostridium difficile* associated diarrhea - use lowest dose and shortest duration where possible		

(Shade Alabi & Jimmy@pharmacyfridaypearls.com

Overview of Evidence			
Author, year	**Design & Sample Size**	**Intervention & Comparison**	**Outcomes**
Daneshmend et al., 1992	Double-blind, placebo-controlled, parallel study (n=1147)	• Omeprazole 80mg IV bolus followed by 40mg IV every 8hr x3, then 40mg PO twice daily vs placebo • Treatment started within 12h of admission, continued for 4 days or until surgery, discharge or death	• **No significant differences between placebo and omeprazole for blood transfusions (53% v 52%), rebleeding (18% v 15%), surgery (11% v 11%) and death (5.3% v 6.9%)** • Significant reduction in signs of UGIB observed during endoscopy with omeprazole (33%) vs placebo (45%); p < 0.0001

Andriulli et al., 2008	Randomized, multicenter double-blind study (n=474)	• PPI Continuous (80mg bolus followed by 8mg/hr infusion for 72hr)
		• PPI Intermittent (40mg IV bolus daily for 72hr)
		  ○ Switched to oral PPI (20 mg twice daily) after 72hr and continued until discharge
		  ○ Used Pantoprazole and Omeprazole
			• **Bleeding recurred in 11.8% continuous regimen vs 8.1% in the intermittent regimen; P = 0.18**
			• 7.6% vs 8.1% rebleeding during first 72hr in the continuous vs intermittent group; P = 0.32
			• Patients in the continuous group had a prolonged hospital stay > 5 days (P = 0.03)

Sung et al., 2009	Randomized, multicenter double-blind study (n=764)	• Esomeprazole 80mg IV bolus followed by 8mg/hr • Placebo, continued for 72hr after endoscopic hemostasis ○ Both groups received esomeprazole PO 40mg daily for 27days after infusion	• **Esomeprazole had less recurrent bleeding within 72hr compared to placebo (5.9% vs 10.3%). Findings remained significant at day 7 and day 30; p = 0.010** • Esomeprazole decreased endoscopic re-treatment (6.4% vs 11.6%), need for surgery (2.7% vs 5.4%) and mortality (0.8% vs 2.1%)
Sreedharan et al., 2010	Systematic review and meta-analysis (6RCTs, n=2223)	• Active treatment with a PPI (oral or IV) and control with either placebo, histamine-2 receptor antagonist or no treatment before endoscopy	• **PPI before endoscopy did not decrease mortality (OR 1.12 95% CI 0.72-1.73), rebleeding (OR 0.81, 95% CI 0.61-1.09) or the need for surgery (OR 0.96, 95% CI 0.68-1.35)** • PPIs significantly decreased the number of patients with stigmata of recent hemorrhage at endoscopy • PPIs compared to control significantly reduced endoscopic intervention
Chen et al., 2012	Prospective, randomized control trial (n=201)	• Pantoprazole 80mg IV bolus then 8mg/hr • Pantoprazole 40mg IV bolus once daily for 72hr ○ Both groups received pantoprazole 40mg daily PO for 27days after 72hr	• **No statistical differences in units of blood transfused, length of hospital stay, surgical/radiological interventions and mortality within 30 days** • High-dose PPI regimen was not superior in the reduction of recurrent bleeding at 30 days as compared with a standard-dose regimen
Sachar et al., 2014	Systematic review and meta-analysis (13RCTs)	• Intermittent doses of PPIs (IV or PO) • 80mg IV bolus followed by 8mg/hr for 72hours	• **Intermittent PPI regimens were comparable and are non-inferior to continuous PPI infusion regimens in patients with bleeding ulcers and high-risk endoscopic findings.** • There is no difference in recurrent bleeding with intermittent vs continuous PPI therapy
Rattanasupar et al., 2016	Prospective, randomized control trial (n=113)	• Pantoprazole 80mg IV bolus then 8mg/hr • Pantoprazole 40mg IV twice daily	• **No difference in average time of hospital stay (3.03 vs 2.89 days, p>0.05) and mean amount of blood transfused (1.79 vs 1.63 units, p>0.05) between continuous and intermittent pantoprazole** • **No statistically significant difference in terms of recurrent bleeding and mortality between both groups (p>0.05)** • Blatchford score greater than 10, 11, and 12 showed high sensitivity of predicting high-risk peptic ulcer bleeding

Conclusions

1. Compared to placebo or other non-PPI treatment measures, evidence suggests PPI therapy did not reduce the need for blood transfusion, rebleeding rate, surgery or death.
2. Compared to placebo, PPIs reduced the signs of upper gastrointestinal bleeding observed during endoscopy and reduced the need for endoscopic treatment.
3. Administration of a PPI as continuous infusion did not impact patient outcomes and is not superior to intermittent therapy; however, high dose PPI may be considered in patients with Blatchford scores greater than 12.

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