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Intermountain Project ECHO TeleCritical Care Medicine

Continuous versus intermittent proton pump inhibitor (PPI) therapy in upper gastrointestinal bleeds

Wednesday, February 2, 2022

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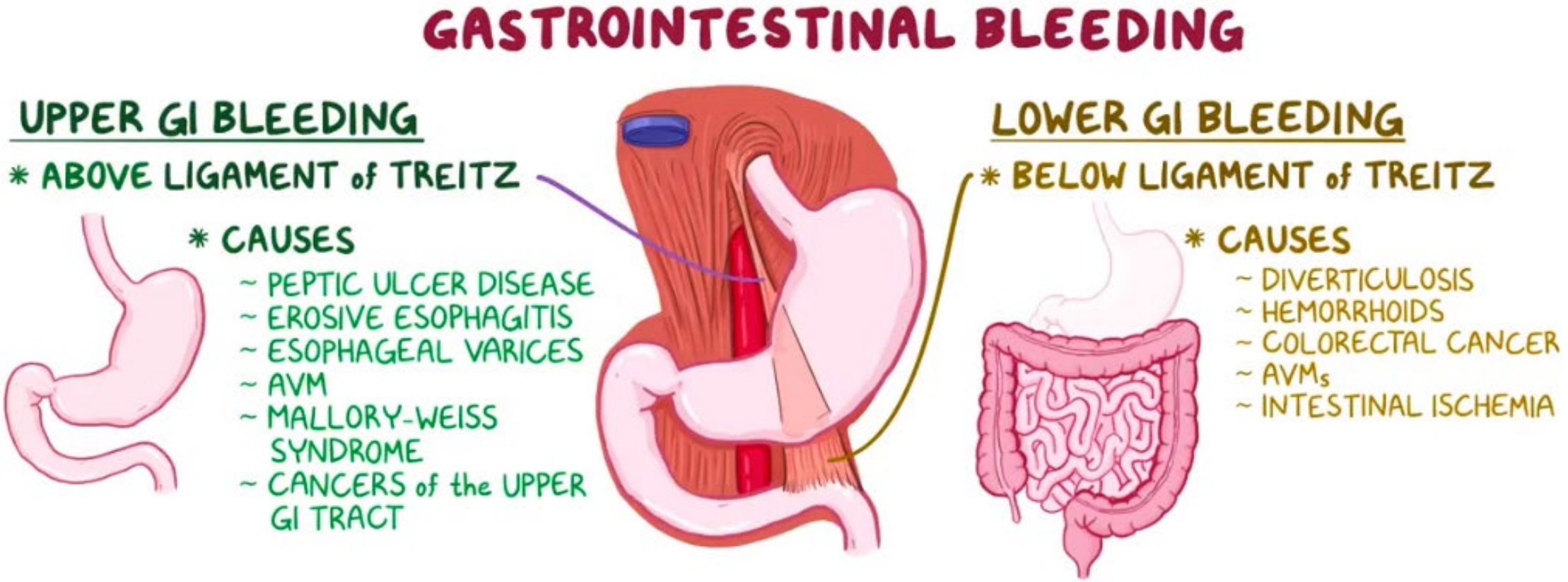
Objectives

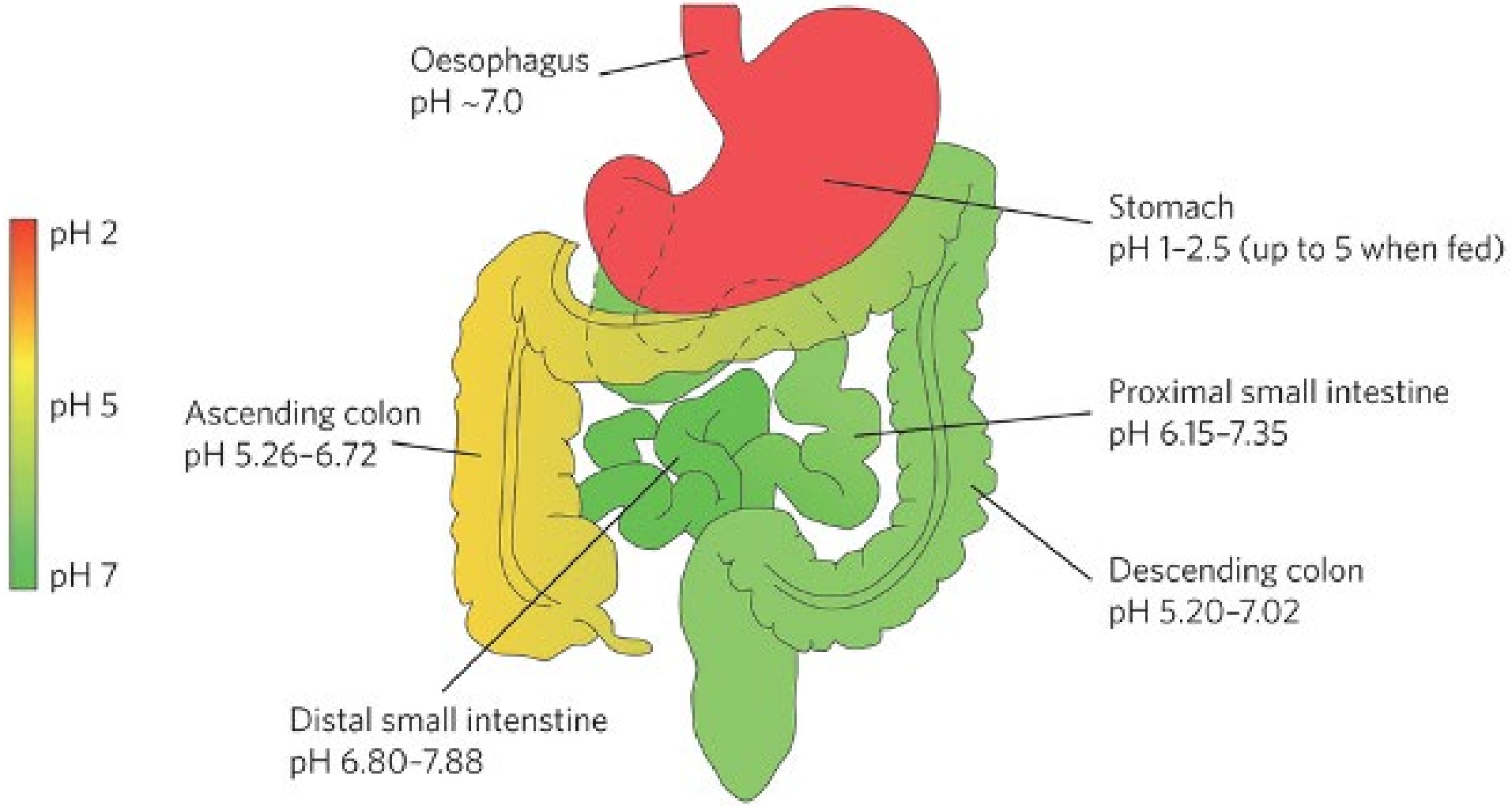
- Analyze literature on PPI dosing in upper GI bleeding
- Summarize updated guideline recommendations

Gastrointestinal (GI) bleeding



Accessed from: https://www.osmosis.org/learn/Gastrointestinal_bleeding:_Clinical_practice

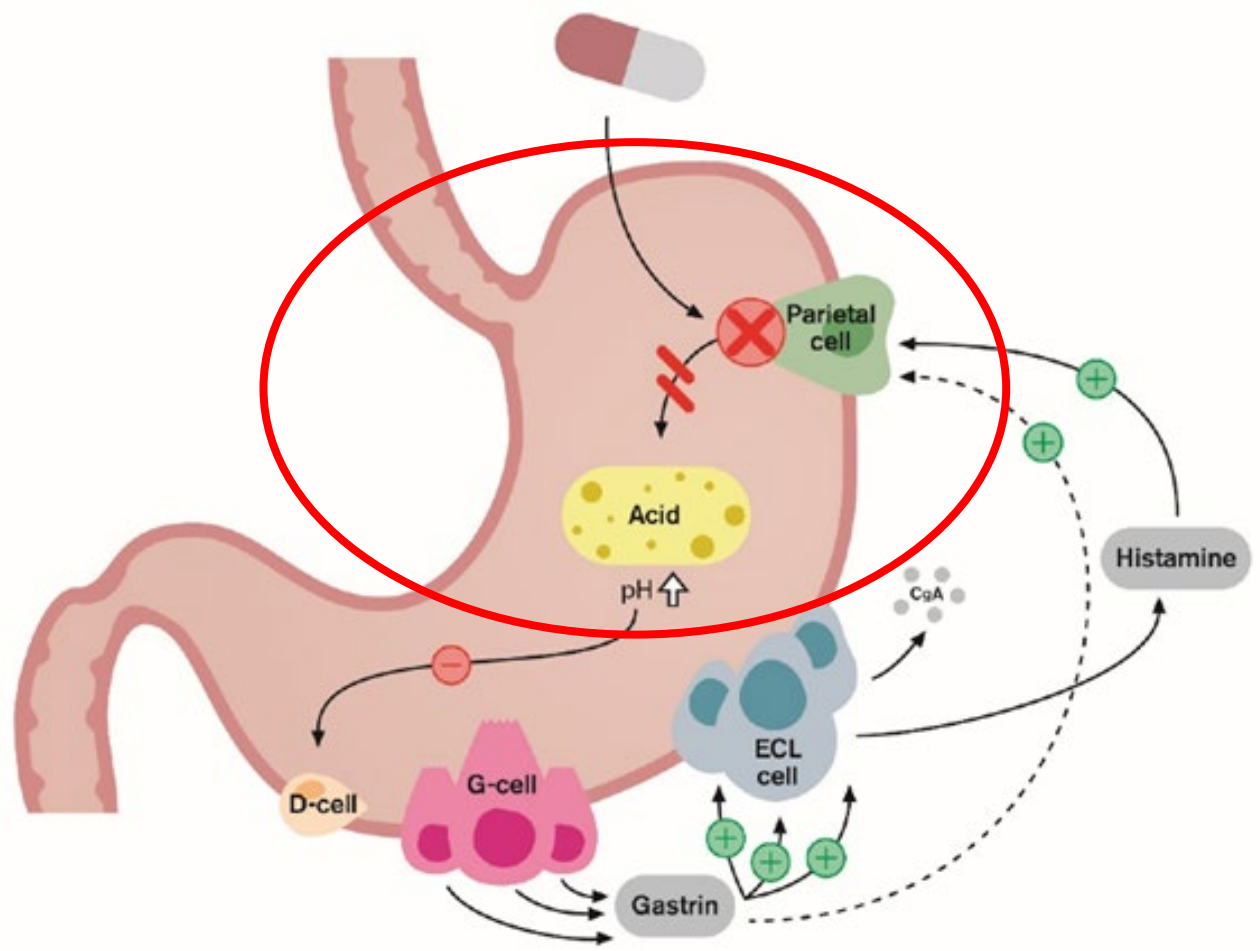
Environment of the GI tract



Green FW, et al. Gastroenterology 1978;74(Suppl 1):38–43.
Zagar SA, et al. Journal of Gastroenterology and Hepatology. 2006; 21:716-721.

Acid suppressive therapy

- Promotes clot formation and further rebleeding
- Optimal pH has not been established
- *In vitro* studies have suggested a pH > 5.4 will promote clot formation and stabilization



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American College of Gastroenterology Guideline Recommendations

2012 Recommendations	2021 Recommendations
After successful endoscopic hemostasis, intravenous PPI therapy with an 80 mg bolus followed by 8 mg/hr continuous infusion for 72 hours should be given to patients who: • Have an ulcer with active bleeding • A non-bleeding visible vessel • An adherent clot	

American College of Gastroenterology Guideline Recommendations

2012 Recommendations	2021 Recommendations
After successful endoscopic hemostasis, intravenous PPI therapy with an 80 mg bolus followed by 8 mg/hr continuous infusion for 72 hours should be given to patients who: • Have an ulcer with active bleeding • A non-bleeding visible vessel • An adherent clot	After successful endoscopic hemostatic therapy of a bleeding ulcer, high-dose PPI therapy should be given continuously OR intermittently for 3 days

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Pantoprazole vs placebo

Zargar et al (N=203)

- Double-blind, placebo controlled, prospective trial
- Pantoprazole 80 mg IV bolus, followed by continuous infusion or placebo in patients with upper GI bleed

	Placebo group ($n = 101$)	Pantoprazole group ($n = 102$)	Relative risk; 95% confidence interval	*P*-value
No. with rebleeding at 2 weeks	20	8	0.35; 0.14–0.82	0.01
At day 3	18	7	0.34; 0.14–0.85	0.02
At day 7	19	8	0.37; 0.15–0.88	0.02
No. requiring urgent surgery	8	3	0.35; 0.09–1.37	0.12
No. requiring rescue therapy	20	8	0.35; 0.14–0.82	0.01
Total no. of rescue therapies	23	9		0.007
Mortality	4	2	0.49; 0.09–2.71	0.45
Mean units of blood transfused (range)				
Total blood transfused	2 ± 3.3 (0–16)	1 ± 2.5 (0–14)		0.003
Before randomization	0.4 ± 0.9 (0–5)	0.4 ± 0.8 (0–4)		0.9
After randomization	1.6 ± 2.6 (0–12)	0.7 ± 1.9 (0–8)		0.0005
Mean hospital stay (days; range)	7.7 ± 7.3 (3–46)	5.6 ± 5.3 (3–42)		0.0003

Zargar SA, et al. Journal of Gastroenterology and Hepatology. 2006; 21:716-721.

Pantoprazole vs placebo

Hung et al (N=168)

- Pantoprazole bolus (80 mg IV x 1) then continuous infusion dosing (8 mg/hr), pantoprazole bolus dosing (40 mg every 12 hours) or placebo in patients with upper GI bleed
- Endpoints included rebleeding rate, transfusion requirements, duration of stay, need for surgical intervention, mortality and gastric pH

	Infusion (n = 54)	No treatment (n = 50)	P
Rebleed, n (%)	2 (3.7)	8 (16.0)	0.034*
Units of pack cells transfused	2.26	2.88	0.244
Operation, n (%)	0	4 (8.0)	0.034*
Total hospital stay (days)	6.37	8.15	0.040*
Mortality, n (%)	0	1 (2)	0.296
Mean pH	5.79	1.46	0.000*
Duration of pH > 6, %	59.0	7.4	0.000*

*Statistically significant.

	Bolus (n = 49)	No treatment (n = 50)	P
Rebleed, n (%)	2 (4.1)	8 (16.0)	0.049*
Units of pack cells transfused	1.53	2.88	0.007*
Operation, n (%)	1 (2.0)	4 (8.0)	0.176
Total hospital stay (days)	6.57	8.15	0.110
Mortality, n (%)	0	1 (2)	0.320
Mean pH	5.26	1.46	0.000*
Duration of pH > 6, %	49.0	7.4	0.000*

*Statistically significant.

Pantoprazole continuous vs intermittent dosing

Hung et al (N=168)

	Infusion (n = 54)	Bolus (n = 49)	P
Rebleed, n (%)	2 (3.7)	2 (4.1)	0.921
Units of pack cells transfused	2.26	1.53	0.098
Operation, n (%)	0	1 (2.0%)	0.291
Total hospital stay (days)	6.37	6.57	0.754
Mortality	0	0	
Mean pH	5.79	5.26	0.069
Duration of pH, %			
>6	59.0	49.0	0.182
>5	78.8	68.1	0.105
>4	85.9	76.8	0.120
>3	91.4	83.4	0.088
>2	96.5	88.5	0.010*
>1	99.7	97.0	0.018*

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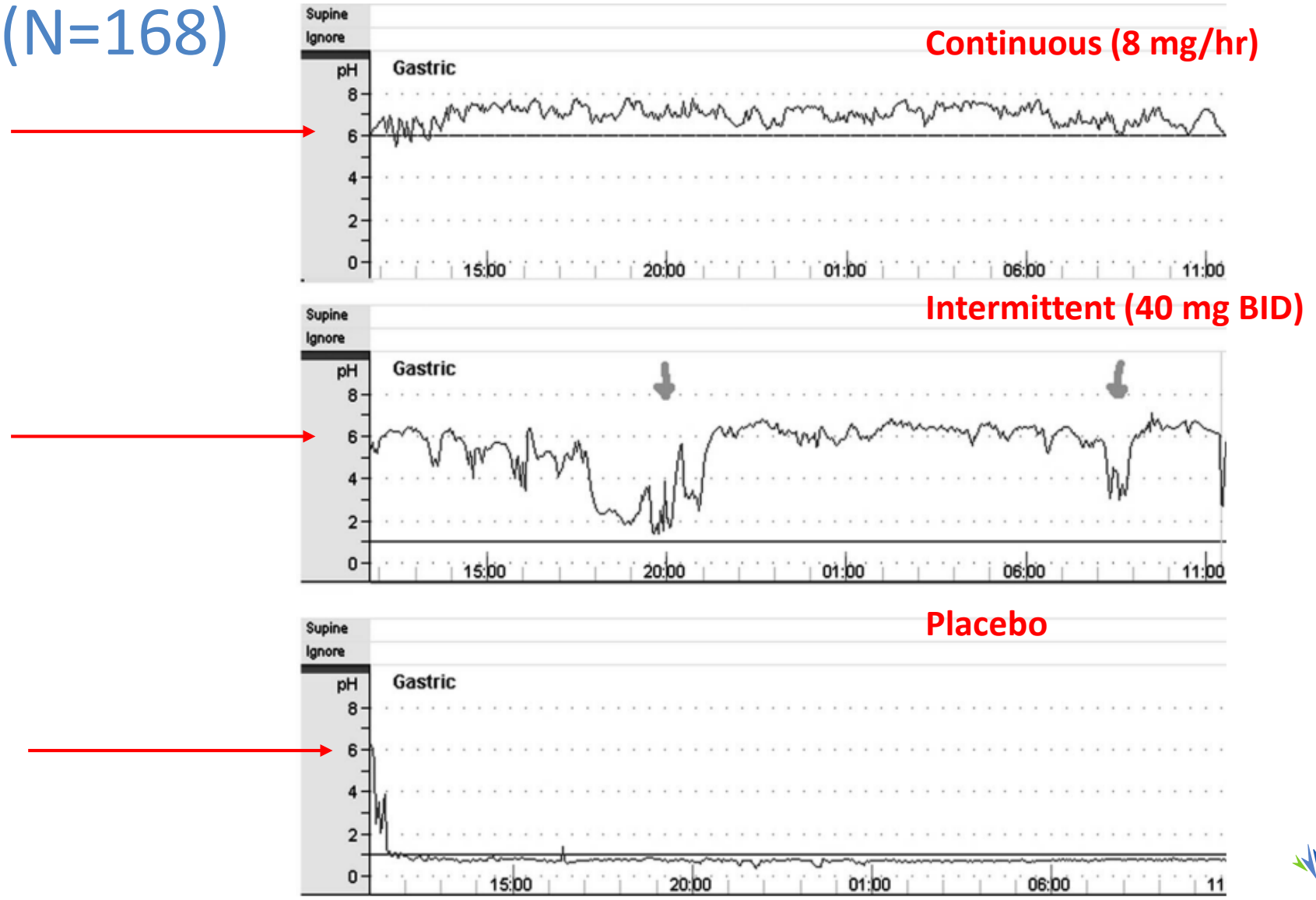
Dosing differences and effect on pH

Hung et al (N=168)



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Continuous vs intermittent dosing

Hsu et al (N=120)

- Open-label, randomized, controlled trial
- Patients received 80 mg IV bolus of pantoprazole followed by either an infusion (8 mg/hr) or bolus (40 mg every 6 hours) for 3 days

	Pantoprazole 192 mg day^{-1} (n = 60)	Pantoprazole 160 mg day^{-1} (n = 60)
Recurrent bleeding (%)	6 (10%)	5 (8.3%)
Hospital stay (days)	9.5 (8.4–10.6)	9.9 (8.3–10.7)
Volume of blood transfusion after therapy (ml)	1179 (487–1995)	1203 (492–2009)
Surgery (%)	1 (1.7%)	0
Death (%)	1 (1.7%)	0

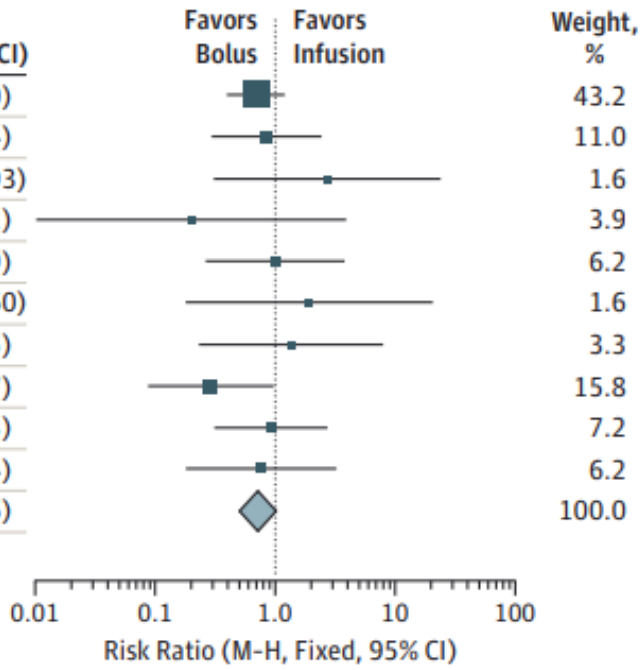
Continuous vs intermittent dosing

Sachar et al (N=1373)

- Systematic review and meta-analysis, only RCT included
- Studies included patients with upper GI bleed with successful endoscopic hemostasis, randomized to intermittent or continuous pantoprazole therapy

Source	Intermittent Bolus, No. Events	Intermittent Bolus, No. Total	Continuous Infusion, No. Events	Continuous Infusion, No. Total	Risk Ratio (M-H, Fixed, 95% CI)
Andriulli et al,[14] 2008	19	239	28	243	0.69 (0.40-1.20)
Chen et al,[16] 2012	6	101	7	100	0.85 (0.30-2.44)
Choi et al,[17] 2009	3	21	1	19	2.71 (0.31-23.93)
Jang et al,[24] 2006	0	19	2	19	0.20 (0.01-3.91)
Javid et al,[20] 2009	4	53	4	53	1.00 (0.26-3.79)
Kim et al,[21] 2012	2	54	1	52	1.93 (0.18-20.60)
Sung et al,[25] 2012	3	105	2	95	1.36 (0.23-7.95)
Ucbilek et al,[26] 2013	3	37	10	36	0.29 (0.09-0.97)
Yamada et al,[22] 2012	4	13	5	15	0.92 (0.31-2.73)
Yüksel et al,[23] 2008	3	49	4	50	0.77 (0.18-3.24)
Total (95% CI)	47	691	64	682	0.74 (0.52-1.06)

Heterogeneity: $\chi^2_9 = 5.96$ ($P = .74$) $I^2 = 0\%$
Test for overall effect: $z = 1.65$ ($P = .10$)



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What do we do now?

Which dosing strategy is best!?

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Additional considerations

Definitive diagnosis

- If its not an upper GIB or ulceration, discontinue PPI

IV access

- Incompatibilities

Duration of therapy

- If short duration expected, intermittent will reduce waste

Cost/drug shortages

Summary

- Proton pump inhibitors (PPIs) are the treatment of choice for upper GI bleeds after endoscopic hemostasis
- Intermittent PPIs are as effective as continuous infusions **AND** can reduce waste and cost

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