Stress Ulcer Prophylaxis in the ICU: Proton-pump Inhibitors

Grand Rounds
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DENVER HEALTH
Level One Care for ALL

Overview

- Background & history
- Who needs intervention
- What treatment is available
- Literature review
- Why proton-pump inhibitors are superior
- Questions & comments

Stress related mucosal injury

- Harvey Cushing – early 1900s
- Hans Selye – "stress ulcer" 1936
- Charles Lucas – GI Bleeds -1971
- Paul Hastings – Acid Suppression - 1978

-Lucas CE. Archives of Surgery. 1971.
- Hastings PR. New England Journal of Medicine. 1978.

How is the mucosa damaged?

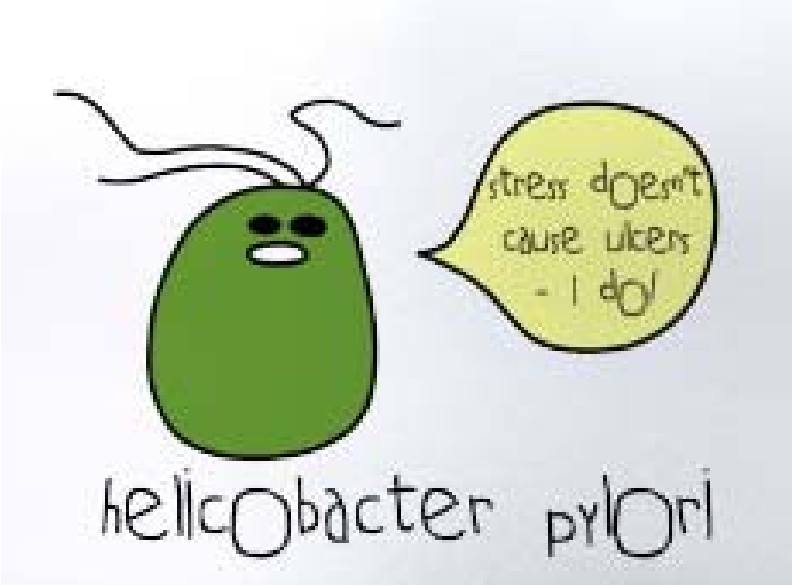
- Ischemic injury + gastric acid
  - Rat studies – gastric blood flow w/ hemorrhage
  - Decreased BP by 40%: lesions
  - Lesion rose in dose dependent fashion, up to 10x, with addition of gastric acid
- Multifactorial – re-perfusion, oxidative stress & oxygen radicals, decreased microcirculation

Ali. Gastroenterology Clinics of North America. 2009.

Who is at risk?

COOK ET AL. NEJM. 1994 – PROSPECTIVE MULTICENTER COHORT STUDY:

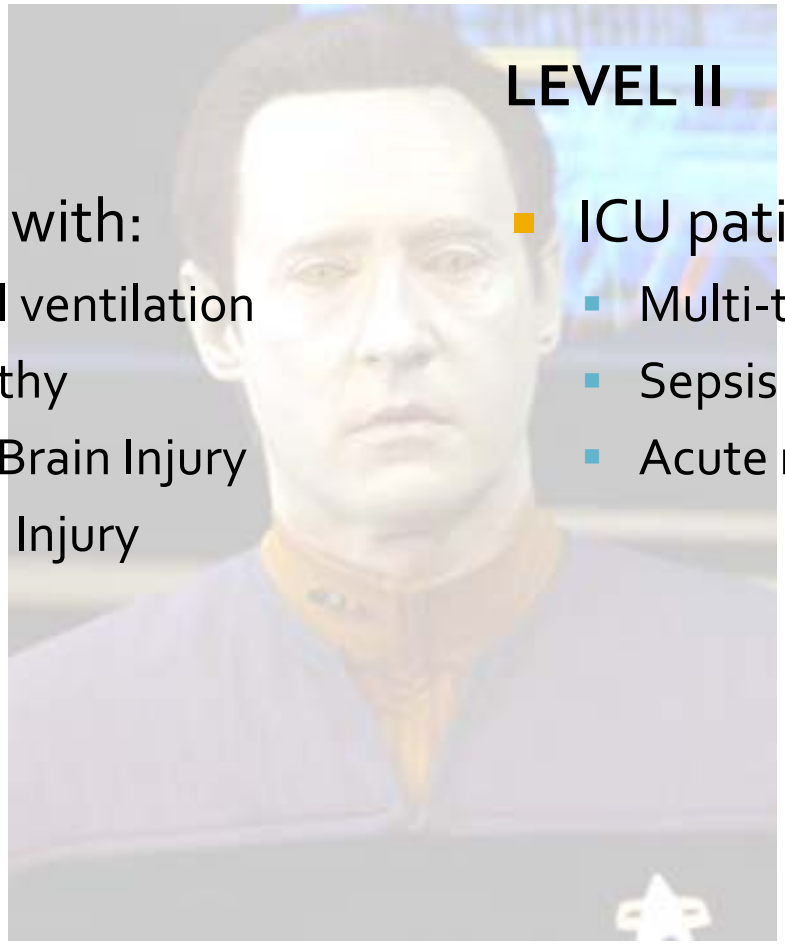
- Overall 1.5% bleeding rate
  - Respiratory Failure
  - Coagulopathy



ELLISON. CRIT CARE MED. 1996. – MULTICENTER COHORT STUDY IN 6 VA HOSPITALS:

- Overall 8% bleeding rate, Mortality 49%
  - Acute hepatic failure
  - Prolonged NGT
  - Alcoholism
  - Renal failure
  - H. Pylori IgA

What does the data say?



LEVEL I

- All patients with:
  - Mechanical ventilation
  - Coagulopathy
  - Traumatic Brain Injury
  - Major Burn Injury

LEVEL II

- ICU patients with:
  - Multi-trauma
  - Sepsis
  - Acute renal failure

Guillamondegui, OG., et al. Eastern Trauma Association Practice Management Guidelines for Stress Ulcer Prophylaxis. 2008

Prophylaxis – which drugs?

- Prophylaxis: reduce mortality by up to 50%

- What are the options?
  - Proton-Pump Inhibitors
  - Sucralfate
  - Histamine-2Receptor Antagonists
  - Others: Misoprostol, Antacids, Early feeding

Cook. JAMA. 1996

What are the drawbacks?

- Acid suppression – increased risk of infection?
  - Nosocomial pneumonia
  - *C. Dificile* diarrhea
- Altered vitamin/mineral/electrolytes
- Drug-Drug interactions
  - H2RA – known cytochrome P450 inhibitors
- Side effects/drug characteristics

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Why are PPIs better?

- Levy et al. Comparison of Omeprazole and Ranitidine for Stress Ulcer Prophylaxis. Digestive Diseases and Sciences. 1998.
  - Prospective, randomized trial of 67 patients

TABLE 3. CLINICAL OUTCOMES*

	Ranitidine	*Omeprazole*	P
Stress ulcer bleed	11 (31%)	2 (6%)	<0.05
Nosocomial pneumonia	5 (14%)	1 (3%)	NS

* Clinically significant bleeding, secondary to stress ulcers, occurred at a statistically significant more frequent rate in those patients receiving ranitidine as compared to omeprazole. Nosocomial pneumonia also occurred more frequently in patients given ranitidine; however, the difference was not statistically significant.

Levy. Digestive Diseases Science. 1997.

Conrad et al. Crit Care Med 2005

- Prospective, double-blind
- Non-inferiority study of omeprazole vs. cimetidine in 359 patients

Table 2. Results in the intent-to-treat population

	Omeprazole Oral Suspension (n = 178)	Intravenous Cimetidine (n = 181)	Confidence Interval for the Difference in Rates, %
Clinically significant bleeding, n (%)	7 (3.9)	10 (5.5)	−100.0, 2.8[a]
Any overt bleeding, n (%)	34 (19.1)	58 (32.0)	−21.9, −4.0[b]
Inadequate pH control, n (%)	32 (18.0)	105 (58.0)	−49.2, −30.9[c]

Any overt bleeding included both end point and non-end point bleeding. Inadequate pH control was defined as two consecutive gastric pH determinations of ≤4 at least 1 hr apart on any given day of treatment; tabulated patients experienced inadequate pH control at least once during the trial. The difference in rates was calculated as omeprazole-cimetidine.

[a]Noninferiority analysis, one-sided 97.5% confidence interval; [b]two-sided 95% confidence interval, $p = .005$; [c]two-sided 95% confidence interval, $p < .001$.

Conrad. Critical Care Medicine. 2005.

Benefits of PPIs

- Do not develop tolerance (vs. H2RAs)
- More consistent pH control (vs. H2RAs, Suc)
- More palatable (vs. Sucralfate)
- More cost effective (Lansoprazole PO vs. IV H2RAs)

-Thomson. World Journal of Gastroenterology. 2010.
-Schupp. Annals of Pharmacotherapy. 2003.

Hospital-acquired pneumonia

- Herzig – JAMA, 2009 – 2219 **NON-ICU** patients underwent subgroup analysis to reveal an increased risk of pneumonia

- Zhou - Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 2010 - meta-analysis of randomized studies of H2RAs vs. PPIs; n=771
  - No difference **10%** vs. 9.9% p=0.89
  - Stress Ulcer Bleeding **2.2%** vs. 6.8% p=0.04

Increased potency

- Lin et al. Crit Care Med 2009.
  - Meta-analysis of randomized controlled trials comparing PPIs vs. H2RAs
  - 936 patients in 7 studies
  - Equivalency of PPIs & H2RAs for bleeding, mortality and pneumonia (p=0.19, p=0.85, p=0.50)
  - Removed Levy et al. from meta-analysis
  - PPIs held pH > 6 more effectively

References

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9. Sung JJ, Barkun A, Kuipers EJ, et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. *Ann Intern Med*. 2009 Apr 7;150(7):455-64. Epub 2009 Feb 16.
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11. Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol.* 2010 May 21;16(19):2323-30.
12. Zhou JF, Wan XY, Huang W, Han LL. [Bleeding and pneumonia in intensive care unit patients given proton pump inhibitor or histamine-2 receptor antagonist for prevention of stress ulcer: a Meta analysis. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2010 Apr;22(4):221-5.
13. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. *JAMA*. 2009 May 27;301(20):2120-8. Acid-suppressive medication use and the risk for hospital-acquired pneumo

Esomeprazole vs. placebo

Table 3. Recurrent Bleeding Rates, Mortality Rates, Surgery, and Hospital Stay

Variable	Esomeprazole Group*	Placebo Group*	*P* Value	Absolute Risk Reduction (95% CI), *percentage points*
Recurrent bleeding, *n* (%)				
Within 72 h				
ITT analysis	22 (5.9)	40 (10.3)	0.026	4.4 (0.6 to 8.3)
PP analysis	14 (4.8)	33 (10.4)	0.009	5.6 (1.5 to 9.8)
Within 7 d	27 (7.2)	50 (12.9)	0.010	5.7 (1.4 to 9.9)
Within 30 d	29 (7.7)	53 (13.6)	0.009	5.9 (1.5 to 10.2)
All-cause mortality within 30 d, *n* (%)	3 (0.8)	8 (2.1)	0.22	1.3 (−0.4 to 2.9)
Bleeding-related mortality within 30 d, *n* (%)	2 (0.5)	3 (0.8)	1.00	0.2 (−0.9 to 1.4)
Surgery within 30 d, *n* (%)	10 (2.7)	21 (5.4)	0.059	2.7 (−0.0 to 5.5)
Repeated endoscopic treatment within 30 d, *n* (%)	24 (6.4)	45 (11.6)	0.012	5.2 (1.1 to 9.2)
Blood transfused within 30 d			0.034	–
Total units	589	935		
Mean units (SD)	1.6 (2.5)	2.4 (4.5)		
Additional hospital days because of recurrent bleeding within 30 d			0.008	–
Total	284	500		
Mean (SD)	0.8 (3.2)	1.3 (3.7)		

ITT = intention-to-treat; PP = per-protocol.
* Esomeprazole group: ITT sample, $n = 375$; PP sample, $n = 292$. Placebo group: ITT sample, $n = 389$; PP sample, $n = 316$.

- Randomized trial of 764 patients in 91 EDs
- Significant reduction in
  - <72H re-bleeds
  - Re-bleed up to 30 days
  - Surgery, mortality, transfusions

Levy. Digestive Diseases Science. 1997.

Costly continuation

- Longitudinal cost analysis of managed care system in PA
- 29,000 patients discharged after hospital stay with risk factors & given PPIs
- 69% discharged with PPI prescriptions

- **$3,000,000 cost to MCO for inappropriate post-discharge PPI prescriptions**

Thomas et al. Journal of Managed Care Pharmacy. 2010.