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A REVIEW OF ACUTE STRESS ULCER PROPHYLAXIS IN THE INTENSIVE CARE UNIT

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It is a well known fact that patients in intensive care unit (ICU) settings are prone to ulcers. Ulcers are generally defined as upper gastrointestinal (GI) in nature and are often secondary to a traumatic event, such as surgery, burns, or a head injury that is critical in nature.[1] These types of ulcers are known as acute stress ulcers. There are other types of ulcers that can be secondary to NSAID use or to a *Helicobacter pylori* infection. Stress ulcers can form very quickly following a traumatic event, sometimes within hours. Recent studies reveal that evidence of acute mucosal damage can be seen within 72 hours of a traumatic event.[2] It must also be noted that only a small percentage of these ulcers will progress to symptoms of acute blood loss.[3]

Although an ulcer is present, many times there are no obvious signs of clinically important bleeding. Signs of clinically important bleeding include hematemesis, hematochezia, or melena complicated by hemodynamic changes. Endoscopy can detect GI bleeds, but many remain undetectable. If clinically important bleeding is present, the patient may present with tachycardia, hypotension, or a decrease in hemoglobin greater than 2 g/dL from baseline. With a large decrease in hemoglobin, a blood transfusion maybe necessary.[1]

Patients may be at higher risk for developing acute stress ulcers depending on several risk factors. The first of which is admission etiology to the intensive care unit. Patients admitted for moderate to severe traumatic events, spinal cord injuries, head injury, thermal burns, organ transplantation or hepatic failure are at an increased risk. Mechanical ventilation greater than 48 hours, platelet count less than 50,000 mm^3, or baseline prothrombin time > 16 seconds, are three additional independent risk factors.[1]

Pathophysiology

Ulcers that form within the first few days generally will form at the more distal region of the gastrointestinal tract. These ulcers are more severe in nature. Both early and late ulcerations form by the same mechanism, and is believed to be due to an imbalance of mucosal protective mechanisms and a hypersecretion of gastric acid. Hypersecretion is caused by over-stimulation of parietal cells by gastrin.[3] This phenomenon is primarily seen in patients suffering from head trauma. The stomach is also protected by a layer of mucus which forms a barrier against hydrogen ion diffusion and is also useful in trapping bicarbonate. This allows acid neutralization in the area nearest to the stomach wall. In patients who suffer a traumatic event, this glycoprotein mucus layer is compromised due to a higher output of bile salts and uremic toxins. Ischemia or poor perfusion also

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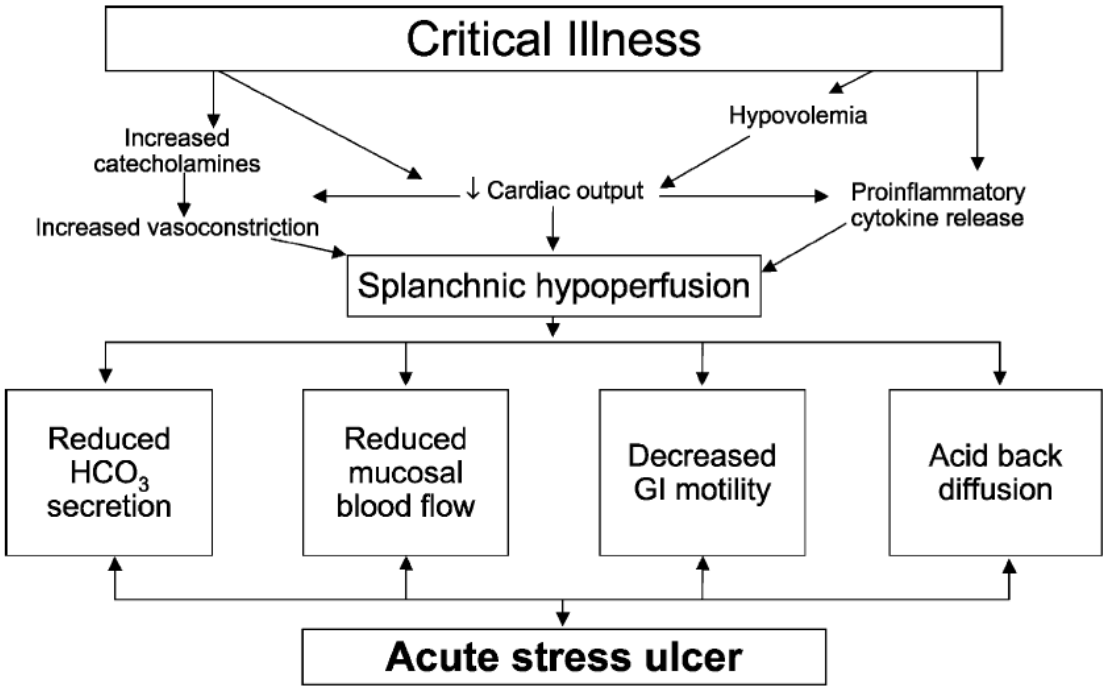
Figure 1. Pathophysiology of acute stress ulcers



Adapted from Stollman N, et al.[17]

plays a role because it will decrease the body's ability to secrete this glycoprotein mucus. This in turn leads to ulceration of the mucosal layer.[3]

H. pylori infections may also play a role in stress ulcer development, although supporting data is limited. In one multi-center case-controlled study, patients infected with *H. pylori* and admitted to an intensive care unit, were more likely to suffer from an acute upper GI bleed than those not infected (36% vs. 16%; p=0.04).[4]

Pharmacology

Proton Pump Inhibitors (PPIs)

Proton pump inhibitors [omeprazole (Prilosec®), lansoprazole (Prevacid®), rabeprazole (AcipHex®), pantoprazole (Protonix®), and esomeprazole (Nexium®)] have the ability to create an environment in the gastrointestinal tract that is favorable for healing. By increasing the pH of the stomach to a level between 4 and 6, PPIs may also decrease the risk of rebleeding. Proton pump inhibitors also have reduced tolerance, especially when compared to H_2 receptor antagonists (H_2RAs). Tolerance of H_2RAs may occur within 24 to 72 hours of use. H_2RAs are not able to maintain a higher pH. At peak effect, H_2RAs may achieve a pH of 5, but will decline to baseline over a few days of treatment.[1]

PPIs are prodrugs; therefore, they must be converted to an active form in order to provide benefit. PPIs are converted to their active form by an acidic environment. Once activated, the molecule will bind to cysteine residues and inactivate H^+, K^+-ATPase, otherwise known as the proton pump. This will systematically stop the function of the proton pump. This mechanism is irreversible and will prevent any hydrogen ions from being transported for the life of the proton pump. The average lifespan of a proton pump is approximately 96 hours. New proton pumps must be created for the secretion of acid to resume.[1]

Proton pump inhibitors have many different dosage forms. (**Table 1**) In the United States, PPIs can be administered in the ICU by IV infusion, suspension, or even encapsulated granules. Tablets and capsules are available for patients able to tolerate an oral diet.

Proton pump inhibitors have many adverse drug reactions, some more serious than others. The incidence of these adverse reactions is quite low, ranging from 1-4%. Some of the more common and less serious adverse effects of PPIs are: abdominal pain, nausea, diarrhea, flatulence, rash, eructation, insomnia, hyperglycemia, and headaches.[5] Drug interactions may also occur with the use of PPIs. Specific interactions may occur with drugs that are metabolized through CYP2C19 and 3A4 and drugs that need an acidic environment for absorption (i.e. azole antifungals and some protease inhibitors).[10]

Table 1. Proton pump inhibitor dosage forms and strengths

Proton Pump Inhibitor (generic)	Dosage forms	Strength
AcipHex® (rabeprazole)	Delayed release tablet	20mg
Nexium® (esomeprazole)	Delayed release tablet	20mg, 40mg
	Delayed release suspension	20mg, 40mg
	IV powder for injection	20mg, 40mg
Prevacid® (lansoprazole)	Delayed release capsule	15mg, 30mg
	Granules for suspension	15mg, 30mg
	IV powder for injection	30mg
	Solutab (orally disintegrating)	15mg, 30mg
Protonix® (pantoprazole)	Delayed release tablet	20mg, 40mg
	IV powder for injection	40mg
Prilosec® (omeprazole)	Delayed release capsule	10mg, 20mg

H_2 receptor antagonists

H_2 receptor antagonists [Cimetidine (Tagamet®), Ranitidine (Zantac®), Famotidine (Pepcid®), Nizatadine (Axid®)] are often used to control peptic ulcer disease, and for the treatment of gastro-esophageal reflux disease (GERD) and dyspepsia. H_2RAs are also used to reduce the incidence of stress ulceration. By blocking H_2 receptors on parietal cells, H_2RAs will inhibit the stimulatory effects and decrease acid secretion.[3] There have been several studies showing the effectiveness of H_2RAs in the setting of stress ulcer prophylaxis. H_2RAs can be given either as an IV bolus or continuous infusion. The use of continuous infusion was shown to maintain higher levels of gastric pH, without decreased rates of bleeding.[2] H_2RAs are also effective when given orally or through a nasogastric tube.[7]

H_2 receptor antagonists are well tolerated and well absorbed. Peak serum concentrations are generally reached 1-3 hours after ingestion. Absorption may be inhibited by approximately 20% if taken with an antacid, but food has no effect. H_2RAs do cross the blood brain barrier and so may have an effect on the central nervous system. These can range from common effects such as headache, to vertigo and lethargy which occur much less frequently.[3]

In randomized clinical trials, H_2RAs adverse effects were not significantly different than placebo.[8] Some rare adverse effects included gynecomastia, impotence, myelosuppression, thrombocytopenia, neutropenia, anemia, pancytopenia, polymyositis, interstitial nephritis, restlessness, somnolence, agitation, headaches, and dizziness.

Antacids

Antacids [Rolaids®, Tums®, Maalox®, and Mylanta®] contain aluminum hydroxide, magnesium hydroxide, or calcium carbonate, and may have combinations of the aforementioned ingredients. Antacids work simply by neutralizing stomach acid. Studies have reported that the use of antacids is effective in preventing stress ulcers, and are roughly equivalent in effectiveness to H_2 receptor antagonsits.[9]

Most antacids are inexpensive and readily available. Administration of antacids becomes problematic due to the high frequency needed for effectiveness. Most antacids need to be administered every 2 hours at a dose of 30 - 60 ml. This can be administered orally or through a nasogastric tube. Many argue that the increased cost of nursing care far outweighs cost saving of antacids.

Common adverse effects of antacids include, hypophosphatemia, hypermagnesemia, constipation, diarrhea, and increased risk of nosocomial pneumonia are some of the adverse reactions seen with antacid use.[10]

Sucralfate

Complex polyaluminum hydroxide salts [sucralfate (Carafate®)] may also be used for ulcer prophylaxis. By coating the gastric mucosa, sucralfate protects the mucosa from overproduction of acid. In the acidic environment of the stomach, sucralfate becomes highly polar where it preferentially binds to exposed ulcer beds; thus, protecting them from further damage from gastric secretions.[6]

The effectiveness of sucralfate is controversial. The most rigorous study found that in 1200 patients being mechanically ventilated, sucralfate increased the risk of GI bleed greater than those patients being treated with an H_2RA, specifically raniti-

dine.[11] There was one meta-analysis that found that sucralfate reduced mortality (though with higher incidences of GI bleed) versus H_2RAs.[12] It is a possibility that this result may be due to a lower incidence of nosocomial pneumonia in the sucralfate population.

Sucralfate is well tolerated and there is little evidence of increased levels of plasma serum aluminum. This result was consistent in patients with renal impairment. Another consideration is the reduced cost of sucralfate compared to PPIs and H_2RAs.[6]

Prostaglandin Analogs

A lesser known option for prophylaxis of stress ulcers are the prostaglandin analogs. Prostaglandin E and I are specifically known to reduce cAMP in parietal cells, effectively inhibiting acid secretion. One of the better known prostaglandin E1 analogs is misoprostol [Cytotec®]. Misoprostol has also been approved by the FDA for the prevention of NSAID-induced ulcers.[6, 10]

It is believed that prostaglandin analogs have antisecretory and cytoprotective effects on the gastrointestinal tract. The cytoprotection afforded by this class of drugs may be due to its ability to reduce acid secretion from the parietal cell, increase bicarbonate and mucus production, and cause vasodilatation in capillary beds, thus decreasing the chance for local ischemia.[10]

There have been several small trials comparing the efficacy of these drugs against H_2RAs and antacids. Most of these trials have shown comparable efficacy, but adverse effects, most notably severe diarrhea, prevent the use of misoprostol in most settings.[13, 14] Misoprostol is contraindicated in women of child bearing age who are not on contraception due to its ability to cause uterine contractions and miscarriage.

Clinical Trials

Although there are clinical trials comparing the efficacy of different prophylactic agents for acute stress ulcers, recent data has suggested that the most effective prophylactic class of drugs are proton pump inhibitors and H_2 receptor antagonists. As such clinical trials comparing the efficacy of proton pump inhibitors and H_2 receptor antagonists will be reviewed.

Omeprazole versus IV cimetidine

This was a non-inferiority analysis designed to show the effectiveness of immediate-release omeprazole in preventing upper gastrointestinal bleeding in critically ill patients.[15] A total of 359 patients in 47 intensive care units were included in the study. These patients were mechanically ventilated for greater than 48 hours, had Acute Physiology and Chronic Health Evaluation score of greater than 11 at baseline. They also had an intact stomach and either a nasogastric or orogastric feeding tube in place. Patients included in the study also had at least one additional risk factor for upper gastrointestinal bleed. These patients were randomized to either 40 mg of omeprazole suspension via either the nasogastric or orogastric tube or IV cimetidine (300 mg bolus, then 50 mg/hr maintenance) for up to 14 days. The pri-

Table 2. Comparison of omeprazole oral suspension to intravenous (IV) cimetidine

	Omeprazole oral suspension (n= 178)	IV cimetidine (n= 181)	Confidence interval for the difference in rates (%)
Clinically significant bleeding, n (%)	7 (3.9)	10 (5.5)	-100 to 2.8[a]
Any overt bleeding, n (%)	34 (19.1)	58 (32)	-21.9 to -4[b]
Inadequate pH control, n (%)	32 (18)	105 (58)	-49.2 to -30.9[c]

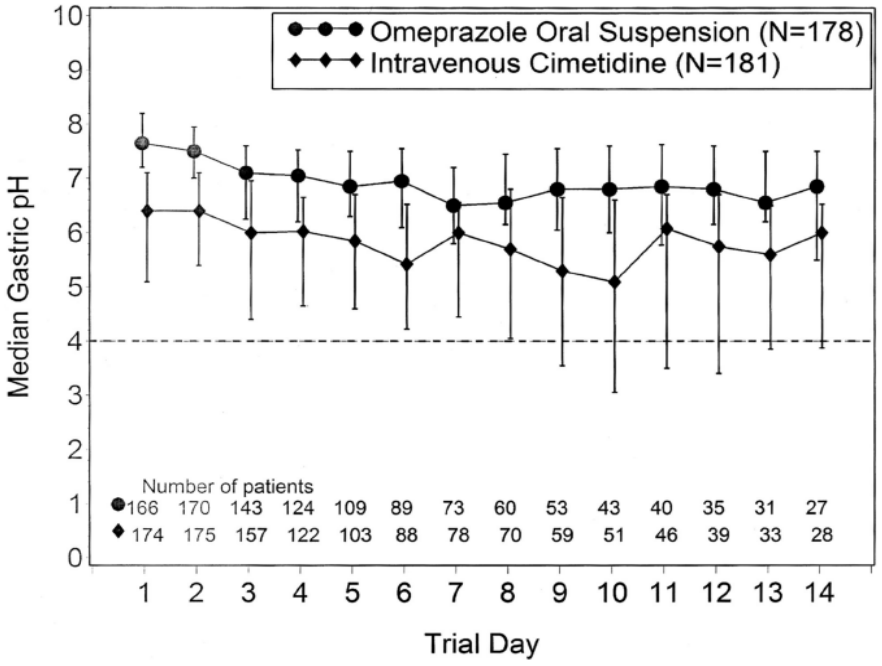
Both end point and non-end point bleeding was included in the definition of any overt bleeding. Inadequate pH control was considered to be two consecutive gastric pH readings of ≤ 4 at least 1 hour apart on any given day of treatment; tabulated patients experienced inadequate pH control on at least one occasion during the trial. The difference in rates was calculated as omeprazole-cimetidine.

[a]Non-inferiority analysis, one-sided 97.5% confidence interval

[b]two-sided 95% confidence interval, p= 0.005

[c]two-sided 95% confidence interval, p< 0.001

Figure 2. Oral omeprazole suspension vs. IV cimetidine on median gastric pH



Adapted from Conrad SA, et al.[15]

mary endpoint was clinically significant upper gastrointestinal bleeding. This was characterized as bright red blood not clearing after 5-10 minutes of lavage or persistent occult–positive coffee ground material for 8 hours on days 1-2 for 2-4 hours on days 3-14 and not clearing with ≥ 100 ml of lavage. The omeprazole suspension treated population showed a 3.9 % rate of clinically significant bleeding versus a 5.5 % rate of clinically significant bleeding in the IV cimetidine group (**Table 2**).

Omeprazole suspension was able to achieve a gastric pH ≥ 6 on all trial days. In the IV cimetidine group, gastric pH ≥ 6 was achieved on only 50% of the trial days. (**Figure 2**) In addition, more patients in the cimetidine group had pH levels below 4. (**Table 3**) This study was able to demonstrate that immediate-release omeprazole suspension is effec-

Table 3. Percentage and number of patients with median gastric pH ≤ 4[15]

Trial Day	Omeprazole oral suspension %	Intravenous Cimetidine, %	*p* value
1	2.4 (4/166)	11.5 (20/174)	< 0.1
2	0.6 (1/170)	10.3 (18/175)	< 0.1
3	2.8 (4/143)	17.8 (28/157)	< 0.1
4	4 (5/124)	13.1 (16/122)	0.01
5	2.8 (3/109)	15.5 (16/103)	< 0.1
6	2.2 (2/89)	20.5 (18/88)	< 0.1
7	1.4 (1/73)	17.9 (14/78)	< 0.1
8	5 (3/60)	24.3 (17/70)	< 0.1
9	3.8 (2/53)	32.2 (19/59)	< 0.1
10	4.7 (2/43)	33.3 (17/51)	< 0.1
11	5 (2/40)	30.4 (14/46)	< 0.1
12	0 (0/35)	25.6 (10/39)	< 0.1
13	0 (0/31)	27.3 (9/33)	< 0.1
14	3.7 (1/27)	28.6 (8/28)	0.02

Table 4. Ranitidine vs. omeprazole in percentage of patients with bleed and pneumonia[16]

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

tive in preventing upper gastrointestinal bleeding and superior to IV cimetidine's ability to maintain a gastric pH > 4 in critically ill patients.[15]

Comparison of Omeprazole and Ranitidine for Stress Ulcer Prophylaxis

This was a prospective, randomized clinical trial designed to compare the efficacy of omeprazole and ranitidine for stress ulcer prophylaxis.[16] The study enrolled 67 high risk patients that were randomized to either receive ranitidine 150 mg (n=35) intravenously daily, or omeprazole 40 mg (n=32) orally or via nasogastric tube daily. These patients were then monitored for clinically important bleeding. Differences in the characteristics of those enrolled, such as gender, race, sex, or age was not statistically significant. The patients were also compared in regard to the severity of their illness based on APACHE II scores, the duration of their ICU stay, duration of ventilator dependency, and mortality rate. There was a significant difference in regards to the number of risk factors for each patient. The ranitidine group had a greater number of risk factors compared to the omeprazole group (2.7 vs. 1.9, $p < 0.05$). In the ranitidine group 11 patients developed clinically significant bleeding versus only two patients in the omeprazole group (31% vs. 6%, $p < 0.05$). In addition, five patients in the ranitidine group developed nosocomial pneumonia versus only one patient in the omeprazole group. (**Table 4**) This secondary outcome was not statistically significant. The authors concluded that omeprazole is clinically safe and effective for the indication of stress ulcer prophylaxis.[16]

Summary

Acute stress ulcers are a common event for patients who have undergone a traumatic event and are admitted to an ICU. They can develop very quickly and may not show any signs of clinically significant bleeding. Patients at high risk, such as those on mechanical ventilation ≥ 48 hrs should be prophylactically treated for acute stress ulcers. There are several pharmacological choices available for treatment. These include antacids, prostaglandin analogs, sucralfate, H_2 receptor antagonists, and proton pump inhibitors. The most commonly studied agents to date have been H_2 receptor antagonists and proton pump inhibitors. While both of these agents have been shown to be effective in recent studies, individual hospital formulary and clinician preference may guide therapy decisions.

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