

Impact of a Multifaceted Intervention on Prescribing of Proton Pump Inhibitors for Stress Ulcer Prophylaxis in the Critically Ill

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Abstract

Background: Lack of well-supported evidence clearly defining one agent as superior to the other for use in stress ulcer prophylaxis (SUP) has led to an array of treatment strategies. Studies comparing histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have shown H2RAs to be non-inferior to PPIs at preventing clinically significant gastric bleeding. This, in addition to the decreased cost associated with H2RAs, has led to the adoption of H2RAs as the preferred agent for SUP at our institution.

Objectives: To evaluate the impact of developing a guideline and removing PPIs from computerized order entry PowerPlans on PPI prescribing for SUP in critically ill patients.

Patients and Methods: Members of the critical care service developed a guideline to direct SUP and removed pantoprazole from two critical care admission PowerPlans. In this interventional study with a historical control, adult patients admitted to the medical or surgical-trauma ICU and prescribed a PPI were evaluated during two time periods before and after the interventions. Patients were excluded if they were receiving a PPI for a reason other than SUP. Patients were assessed daily for an indication for SUP. These included mechanical ventilation, high dose steroids, and coagulopathy.

Results: A total of 92 and 60 patients were included in the pre- and post-intervention groups, respectively. PPI use for SUP was reduced from 38% in the pre-intervention group to 15.6% in the post-intervention group ($P < 0.0001$). PPI days adjusted for LOS were not different between the pre- and post-intervention groups (84% vs 86%, $P = 0.5909$). Of the total PPI days, 52.4% (95% CI 48.8 - 56.1) were classified as inappropriate because there was no indication, while the remaining 47.6% (95% CI 43.9 - 51.2) had an indication but should have received a H2RA. The total cost associated with guideline non-adherence was \$1802.

Conclusions: Our multifaceted intervention reduced the number of days in which a PPI was prescribed for SUP in the overall ICU population; however, it did not impact the duration of PPI therapy. Patients either had no indication for SUP, or had an indication where less costly H2RAs could have been used. Additional opportunity exists to improve cost-effective prescribing of SUP for critically ill patients.

Keywords: Critical Illness; Proton Pump Inhibitors; Histamine H2 Antagonists

1. Background

Stress-related mucosal disease can be detrimental to critically ill patients, further complicating an already unstable clinical picture. This condition results from placing an individual under abnormally elevated physiological demands, ultimately leading to splanchnic hypoperfusion and the formation of an acute stress ulcer (1). Disease severity can range from endoscopic evidence of mucosal damage to clinically significant bleeding. Larger studies assessing the presence of mucosal damage report prevalence rates of any extent of damage in roughly 75% - 100% of critically ill patients, while clinically significant bleeding occurs on average in < 0.5% - 6% of patients (2-5). Risk factors associated with the development of stress-related mucosal disease have been recognized, including

continuous mechanical ventilation for greater than 48 hours and coagulopathy (1).

Stress ulcer prophylaxis (SUP) has been a topic of much debate in critically ill patients for an extended period of time. Lack of well-supported evidence clearly defining one agent as superior to the other has led to a wide array of treatment strategies adopted by institutions around the country. Medications used for SUP are not benign and, as most medications, are associated with side effects (4). For this reason, routine SUP for every critically ill patient is not recommended. Recent studies have focused on comparing two classes of acid suppressing therapies: histamine-2 receptor antagonists (H2RA) and proton pump inhibitors (PPI). A majority of studies comparing

these medication classes have shown H2RAs to be non-inferior to PPIs at preventing clinically significant gastric bleeding, while demonstrating a decreased incidence of secondary complications including Clostridium difficile infection and pneumonia (4, 6, 7). PPIs are known to have superior acid suppression when compared to H2RAs, which may be related to the increase in secondary complications (6, 8). Lastly, the agents differ in cost with PPIs being more expensive than H2RAs (7).

In response to the lack of evidence demonstrating one agent as superior to the other and the higher cost and increased incidence of secondary complications associated with PPIs, the critical care service line at Carolinas Medical Center (CMC) chose to adopt the H2RA famotidine as the agent of choice for SUP.

2. Objectives

We sought to evaluate the impact of a multifaceted intervention on PPI prescribing patterns for SUP in critically ill patients.

3. Patients and Methods

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the CMC institutional review board. The need for informed consent was waived since neither routine patient care nor the administration of stress ulcer prophylaxis was modified for the purposes of this study.

3.1. Intervention

Our intervention consisted of two components that occurred in sequential order (Figure 1). Initially, multi-professional members of the critical care service developed a guideline for the use of SUP in the ICU population. The guideline was centered around the presence of clinical indications selected as risk factors for SUP based on expert discussion and literature review. Buy-in was obtained via presentation at and approval by the Carolinas Healthcare System, Critical Care Quality, Safety, and Operations Council. For the purposes of this study, evaluations were based on an adapted guideline (Figure 2). Changes were then made to two power plans (computerized order sets) to reflect the guideline recommendation of famotidine as the preferred pharmacological agent. Specifically, a critical care clinical pharmacist submitted a request to remove pantoprazole from the stress ulcer prophylaxis section of the adult trauma admission critical care and adult critical care admission PowerPlans. The institution's evidence based care team followed a standardized process for approval and implementation of this change. For the adult trauma admission critical care PowerPlans, a priority 2 (non-emergent) process was followed in which approval was obtained by a subject matter expert and education was conducted over a two-week time period. This change was completed in April 2014. For the adult critical care admission PowerPlan, a priority 3 (regular periodic review)

process was followed in which the revised PowerPlan was posted for a two week comment period, a review of comments by Subject Matter Experts was conducted, and education was provided over a two-week time period. This change was completed in May 2014.

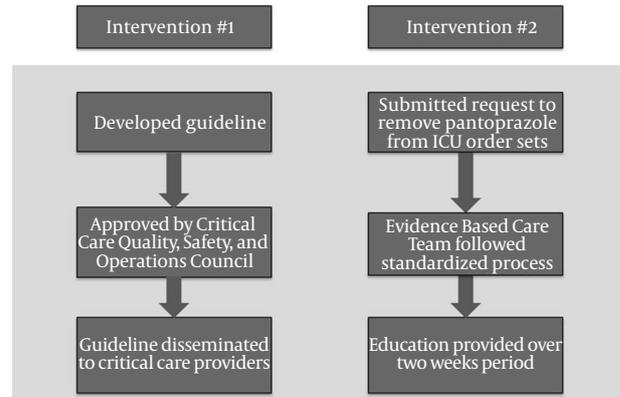


Figure 1. Process of Implementing the Multifaceted Intervention

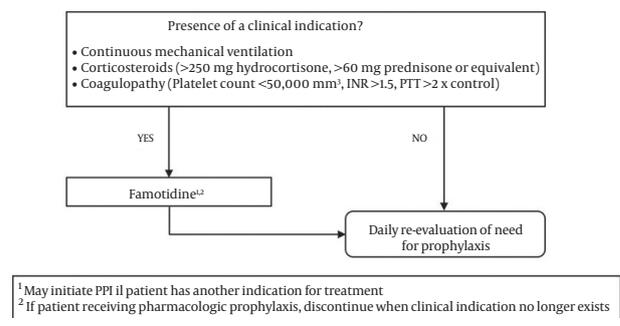


Figure 2. Adapted Critical Care Guideline for Stress Ulcer Prophylaxis

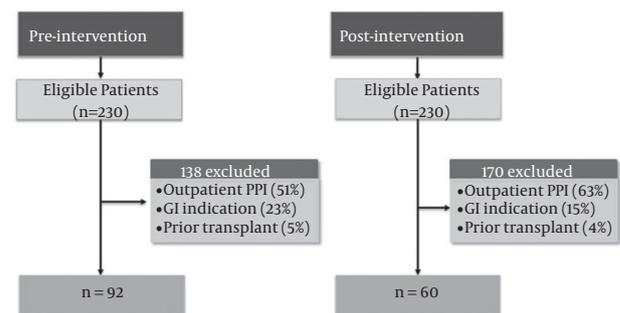


Figure 3. Enrollment

3.2. Data Collection

The timeframes for data collection in the pre- and post-intervention groups were February 4 - 28, 2014 and December 2014, respectively. A report was generated daily to identify patients >18 years of age admitted to the medical intensive care unit (MICU) or surgical-trauma intensive care unit (STICU) with an active order for a PPI. The

formulary PPI for intravenous use is pantoprazole (Protonix; Pfizer, New York). PPIs available for via tube and oral use include lansoprazole (Prevacid SoluTab; Takeda, Deerfield) and omeprazole (Prilosec; Astrazeneca, Wilmington), respectively. Patients were excluded if they had another indication for receiving a PPI which included outpatient PPI therapy, active gastrointestinal bleeding or ulceration, gastritis, duodenitis, esophageal surgery, or previous solid organ transplant. Patients included in the study were assessed daily for indications for SUP per the guideline.

The electronic medical record (EMR) was used to identify demographic information. Subjects in the control group with an active GI bleed, ulceration, gastritis, duodenitis, or a previous solid organ transplant were identified by the respective disease state classifications according to the International Classification of Diseases, Ninth Revision (ICD-9) Table S1; these data points were collected directly from the EMR for the post-intervention group. Select data points, including ICU length of stay (LOS), were extracted from the EMR for both cohorts by a data analytics group. All other information including proton pump inhibitor therapy (agent, duration of treatment), mechanical ventilation, high dose corticosteroids, platelets, international normalized ratio (INR), partial thromboplastin time (PTT), esophageal surgery, and solid organ transplant was collected directly from the EMR by the study investigator on a daily basis.

The acquisition cost of PPIs was used to calculate cost associated with use of a non-preferred therapy. These include: pantoprazole 40 mg injection, \$2.88; lansoprazole 30 mg oral disintegrating tablet, \$7.94; lansoprazole 15 mg oral disintegrating tablet, \$7.94; omeprazole 20 mg capsule, \$0.14.

3.3. Statistical Methods

Descriptive statistics, including means and standard deviations, and counts and percentages, were calculated. The pre- and post-intervention groups were compared on baseline and demographic variables using Student's t-test for interval data, the Wilcoxon rank sum test for ordinal data, and the chi-square test or Fisher's exact test for categorical data. The primary analysis was a Poisson regression comparing the pre- and post-intervention groups on the number of days a PPI was prescribed for

SUP per ICU census days, as well as the number of days a PPI was prescribed per patient ICU length of stay. The Chi-square test was used to compare the two groups on the percentage of patients with no indication for SUP and the percentage of patients with an indication for SUP but receiving a non-preferred agent. SAS®, Enterprise Guide® 5.1 was used for all analyses. A two-tailed p-value of less than 0.05 was considered statistically significant.

3.4. Outcomes

The primary outcomes were the percentage of patient days receiving a PPI for SUP (calculated as number of days receiving a PPI divided by total ICU census days) and the percentage of the LOS receiving a PPI (calculated as number of days receiving a PPI divided by the LOS in days). Secondary outcomes were targeted at evaluating compliance with the guideline. These included the percentage of days with no indication for SUP, as well as percentage of days with an indication for SUP but receiving a PPI (non-preferred therapy). Additionally, cost associated with non-preferred PPI use was evaluated.

4. Results

During the two study periods, 460 patients had an active order for a PPI (Figure 3). Of these, 138 and 170 patients were excluded in the pre- and post-intervention groups, respectively. The most common reason for exclusion in both cohorts was outpatient PPI therapy. Of the patients excluded for either gastric bleeding or ulceration, gastritis, duodenitis, or esophageal surgery, 56% were also prescribed a PPI as outpatient therapy. A total of 92 and 60 patients were included in the pre- and post-intervention groups, respectively. This cohort consisted of patients who were receiving a non-preferred agent (PPI) for the sole indication of SUP. Baseline characteristics were similar between groups (Table 1).

A reduction in the percentage of PPI use for SUP was observed from 38% (490 PPI days per 1290 ICU census days) in the pre-intervention group to 15.6% (246 PPI days per 1578 ICU census days) in the post-intervention group ($P < 0.0001$). In contrast, once a PPI was prescribed for SUP, the duration of use was unchanged between groups as demonstrated by a similar percentage of PPI days per ICU LOS (84% vs 86%, $P = 0.5909$). Of the total PPI days among both the pre- and post-intervention groups, 52.4% (386/736;

Table 1. Characteristics of the Study Population^{a,b}

Variable	Pre-intervention (n = 92)	Post-intervention (n = 60)	P Value
Gender (male)	44.6% (41/92)	51.7% (31/60)	0.3914
Age, y	63 (17)	58 (22)	0.0751
Length of stay, d	4 (5.5)	3 (3.5)	0.0931
Length of mechanical ventilation, d	1 (3)	1 (3)	0.7272

^aGender results presented as % of group (frequency).

^bAll other results are median (IQR).

95% CI 48.8 - 56.1) were classified as inappropriate because there was no indication for SUP present, while the remaining 47.6% (350/736; 95% CI 43.9 - 51.2) had an indication but should have received a H2RA. The total cost associated with guideline non-adherence was \$1,145 in the pre-intervention group and \$657 in the post-intervention group.

5. Discussion

The interventions in this study were implemented as part of an initiative to optimize SUP and were designed to reduce the non-preferred use of PPIs. A multifaceted approach of developing a guideline and removing PPIs from computerized order sets resulted in a decrease in their overall use, but did not impact duration of therapy. There are a number of potential explanations for these findings.

Several studies describe guideline development to facilitate compliance with institutional recommendations. One study that sought to reduce non-preferred use of SUP through an algorithm-based intervention demonstrated similar outcomes to ours; a reduction in overall inappropriate prescribing but no effect on the duration of therapy once prescribed (6). Another study demonstrated a 12% reduction in inappropriate prescribing (19% to 6.6%) through the incorporation of an institutional guideline in combination with an educational component (9). Guidelines alone are not entirely successful at directing physician prescribing. Reasons for non-compliance are widespread and commonly include unawareness, unfamiliarity, and disagreement (10). Regarding disagreement, the primary literature deserves mention. While the majority of clinical trials demonstrate the non-inferiority of H2RAs at preventing clinically significant gastric bleeding, some suggest that PPIs are a preferred treatment option (5, 11).

In an effort to enhance guideline compliance, we modified the ICU admission order sets to reflect our guideline recommendations. Standardization using computerized prescriber order entry (CPOE) technology has influenced prescribing, resulting in reduced costs and improved out-

comes (12). To our knowledge, ours is the only study that evaluates the use of CPOE to optimize SUP prescribing.

Our secondary outcomes demonstrated that reasons for non-compliance were multifactorial; patients were receiving SUP despite not having an indication per the guideline and patients with an indication were receiving non-preferred therapy. Further education focused on guideline awareness may be required to increase compliance. Education would improve guideline awareness and familiarity but would not affect disagreement with recommendations. In addition, educational interventions tend to yield short-lived benefit and are not an effective measure for producing long-term sustainability (13).

Additional intervention is needed to further reduce the use of PPIs for SUP at our institution. One potential strategy to hard-wire prescribing includes restricting PPIs to specific indications via the computerized order entry system. The development of a pharmacist-directed stewardship program may reduce PPI prescribing but would require additional resources. The cost-effectiveness of such a program would require evaluation.

Several factors limit the generalizability of our findings to other institutions. First, this was a single center study conducted in two specialized ICUs at our institution. Second, we did not control for differences in provider practices or the presence of clinical pharmacists on rounds, nor did we investigate specific reasons for guideline non-compliance. Another limitation is that we used ICU census days to control for all opportunities of PPI use for SUP. This limited our ability to determine if the reduction in overall PPI use was attributed to an increased use of famotidine or rather a reduction in the total number of ICU patients receiving SUP. A more precise way of evaluating this outcome would be to assess all ICU patients for an indication for SUP and directly compare differences in the use of famotidine versus PPIs. Finally, it is possible that our exclusion criteria did not account for all reasons (other than SUP), that a PPI may be indicated. We attempted to establish a comprehensive list through the utilization of ICD9 codes (S1); however, we realize other indications may have been present.

Table S1. ICD9 Codes Used for Patient Exclusion

Condition	ICD9 Code
Gastrointestinal hemorrhage	578.0, 578.1, 578.9
Gastric ulcer	531.0, 531.00, 531.01, 531.1, 531.10, 531.11, 531.2, 531.20, 531.21, 531.3, 531.30, 531.31, 531.4, 531.40, 531.41, 531.5, 531.50, 531.51, 531.6, 531.60, 531.61, 531.7, 531.70, 531.71, 531.9, 531.90, 531.91
Peptic ulcer	533.0, 533.00, 533.01, 533.1, 533.10, 533.11, 533.2, 533.20, 533.21, 533.3, 533.30, 533.31, 533.4, 533.40, 533.41, 533.5, 533.50, 533.51, 533.6, 533.60, 533.61, 533.7, 533.70, 533.71, 533.9, 533.90, 533.91
Gastrojejunal ulcer	534.0, 534.00, 534.01, 534.1, 534.10, 534.11, 534.2, 534.20, 534.21, 534.3, 534.30, 534.31, 534.4, 534.40, 534.41, 534.5, 534.50, 534.51, 534.6, 534.60, 534.61, 534.7, 534.70, 534.71, 534.9, 534.90, 534.91
Gastritis/duodenitis	535.0, 535.00, 535.01, 535.1, 535.10, 535.11, 535.2, 535.20, 535.21, 535.3, 535.30, 535.31, 535.4, 535.40, 535.41, 535.5, 535.50, 535.51, 535.6, 535.60, 535.61, 535.7, 535.70, 535.71
Duodenal ulcer	532.0, 532.00, 532.01, 532.1, 532.10, 532.11, 532.2, 532.20, 532.21, 532.3, 532.30, 532.31, 532.4, 532.40, 532.41, 532.5, 532.50, 532.51, 532.6, 532.60, 532.61, 532.7, 532.70, 532.71, 532.9, 532.90, 532.91

A multifaceted approach of developing a guideline and removing PPIs from computerized order sets resulted in a decrease in their overall use, but did not impact duration of therapy. Patients either had no indication for SUP, or had an indication where less costly H2RAs could have been used. Additional opportunity exists to improve cost-effective prescribing of SUP for critically ill patients at our institution.

Footnotes

Author' Contributions: Study concept and design: Gail Gesin, Matthew Joseph Morrisette, John Michael Hammer, Harry James Norton, William Edward Anderson, and Michael Brian Green. Acquisition of data: Matthew Joseph Morrisette. Analysis and interpretation of data: Matthew Joseph Morrisette, Gail Gesin, John Michael Hammer, Harry James Norton, and William Edward Anderson. Drafting of the manuscript: Matthew Joseph Morrisette. Critical revision of the manuscript for important intellectual content: Gail Gesin and John Michael Hammer. Statistical analysis: Harry James Norton and William Edward Anderson. Study supervision: Gail Gesin and John Michael Hammer.

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