

Inappropriate Use of Proton Pump Inhibitors for Stress Ulcer Prophylaxis

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This review of proton pump inhibitor use at a large VA medical center identified preventable annual costs of over \$160,000 and found significant associations between inappropriate long-term therapy and development of *Clostridium difficile*-associated disease.

Stress-related mucosal disease (SRMD) is characterized by acute multiple ulcerations of the upper gastrointestinal submucosa, which may be either diffuse or focal, superficial or deep.^{1,2} SRMD can result from any number of factors that increase physiologic demands, though the most common etiology is splanchnic hypoperfusion resulting in gastric mucosal ischemia.^{3,4} Patients in intensive care units (ICUs), who are at elevated risk for splanchnic hypoperfusion, are prone to developing stress ulcers and associated gastrointestinal bleeding.

When Cook and colleagues evaluated risk factors for stress ulcer in 2,252 patients admitted to ICUs, they found that respiratory failure requiring mechanical ventilation for more than 48 hours and coagu-

lopathy were strong independent risk factors for clinically significant gastrointestinal bleeding.⁵ In light of such findings, guidelines from the American Society of Health-System Pharmacists (ASHP) Commission on Therapeutics recommend administering stress ulcer prophylaxis (SUP) to patients who are admitted to an ICU and have 1 of the following risk factors: coagulopathy, mechanical ventilation for more than 48 hours, or a history of gastrointestinal ulceration or bleeding within the year prior to admission.⁶ In addition, SUP is recommended for patients with 2 of the following risk factors: sepsis, ICU stay longer than 1 week, occult bleeding of at least 6 days duration, or use of high-dose corticosteroids (hydrocortisone ≥ 250 mg/day, or the equivalent).^{2,6-9} Recommended SUP includes using acid suppressive therapy (AST), such as a proton pump inhibitor (PPI) or histamine-2 blocker, to reduce gastric acid secretion and allow for gastric healing.⁶ For patients in general medicine units, however, neither the ASHP guidelines nor current literature support the routine use of AST as SUP, because it provides no clear benefit for this population. Nevertheless, many providers use these agents for this indication.

A retrospective chart review of 213 newly admitted non-ICU patients found that 29% were using AST be-

fore admission and that this figure jumped to 71% after admission, though only 10% of AST users had an appropriate indication.¹⁰ Another study found that 54% of 226 patients admitted to a general medical nursing unit were using AST upon admission, 65% of whom had no indication, and 55% of patients prescribed AST for SUP still were using the therapy at discharge.¹¹

Not only does the inappropriate use of AST within hospitals and after discharge represent unnecessary costs, it may result in unforeseen complications. The reduction of gastric acid secretion caused by PPIs can impair patients' defense against ingested pathogens, thereby increasing their risk of gastric and respiratory infection.^{12,13} Researchers recently have investigated a possible association between long-term use of PPIs and community-acquired *Clostridium difficile*-associated disease (CDAD),^{14,15} which can produce a wide variety of outcomes, ranging from mild diarrhea to pseudomembranous colitis and death.¹⁶

OBJECTIVES

The primary objectives of this study were to determine the percentage of patients prescribed PPI therapy for SUP while being treated on a general medicine unit, the percentage of patients discharged with a PPI prescription for SUP, and the associated

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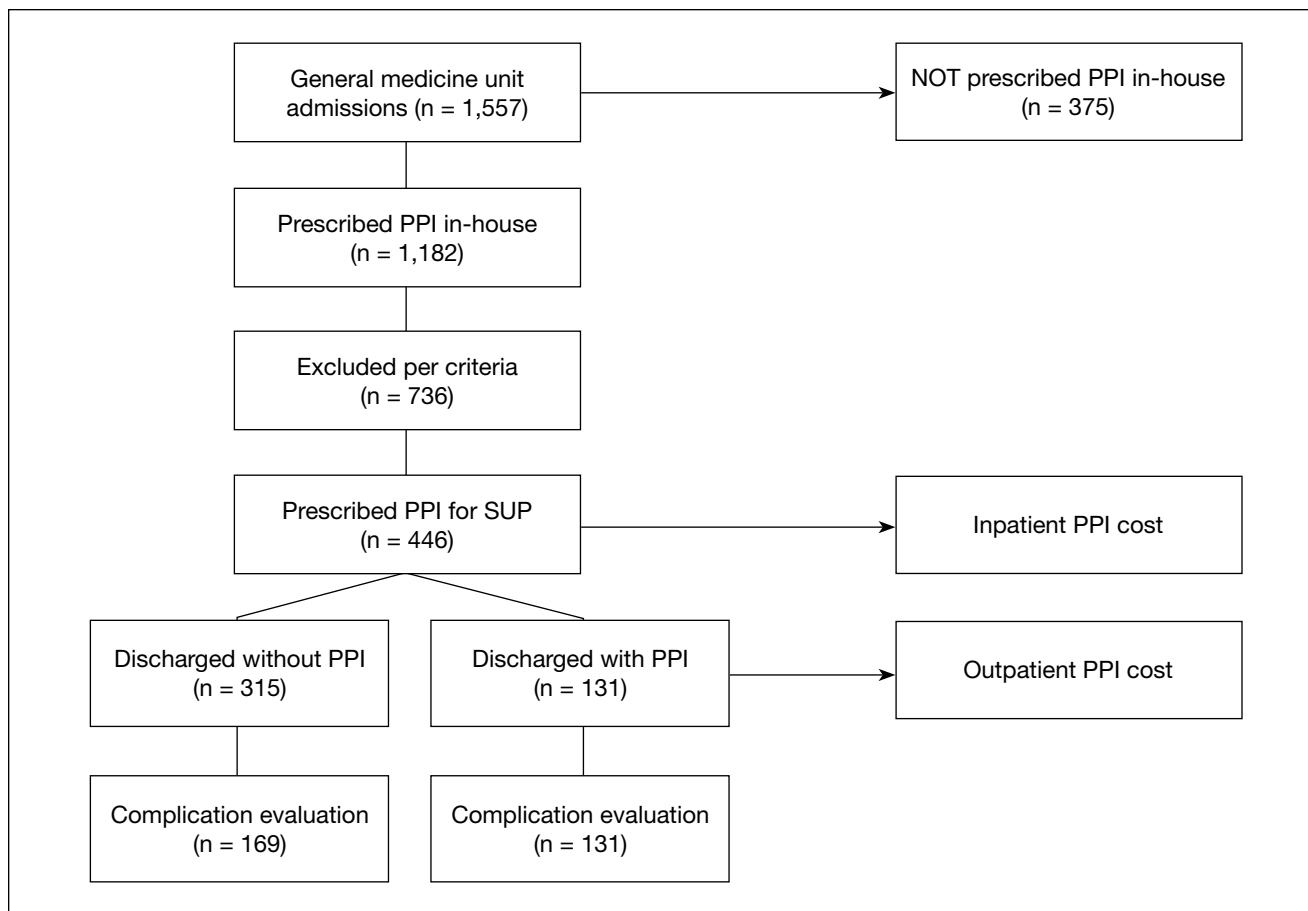


Figure. Study outline. Patients were included if prescribed a PPI for SUP while being treated in a general medicine unit and excluded if they were receiving outpatient PPI treatment prior to admission, transferred from an intensive care unit or an outside hospital, or prescribed a PPI for any of the following reasons: as prophylaxis for gastropathy associated with nonsteroidal anti-inflammatory drugs; for a diagnosed gastrointestinal bleed; or for an FDA-approved indication, such as gastroesophageal reflux disease, active ulcer disease, erosive esophagitis or gastritis, as part of a multidrug regimen for *Helicobacter pylori* eradication, or for a pathologic hypersecretory condition.¹⁶ Complication evaluation = group of patients used to evaluate complication of CDAD associated with PPI; PPI = proton pump inhibitor; SUP = stress ulcer prophylaxis.

economic inpatient and outpatient utilization costs. The secondary objective was to compare the incidence of new onset CDAD among patients discharged with and without prescribed PPI therapy for SUP. The use of the VA's advanced Computerized Patient Record System (CPRS) enabled us to accurately track PPI utilization within a single cohort transitioning from inpatient to outpatient care.

MATERIALS AND METHODS

All research was conducted with the approval (and in compliance with the requirements) of the Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals and the VA Research and Development Committee. The study site, a large VA medical center, serves as the primary health care provider for more than 120,000 veterans in southeast Texas. This 375-bed facility includes 163 general

medicine beds, 52 intensive care unit beds, a 40-bed spinal cord injury center, and a 120-bed transitional care unit for long-term care.

Subjects and study design

In this single-center, retrospective, medical record review, we used the VA's CPRS to identify all patients who had been admitted to the general medicine units between May 1, 2006, and July 31, 2006, and were prescribed a PPI for SUP, as recorded in

Table 1. Study criteria

Inclusion	Exclusion
<p>Prescribed a PPI while treated on a general medicine unit</p> <p>Prescribed a PPI for SUP</p>	<p>Received a PPI within the 8 weeks immediately prior to admission</p> <p>Transferred from a critical care unit</p> <p>Transferred from an outside hospital</p> <p>Prescribed a PPI for an appropriate indication:</p> <ul style="list-style-type: none"> • gastroesophageal reflux disease • active ulcer disease • erosive esophagitis or gastritis • as part of a regimen for <i>Helicobacter pylori</i> eradication <p>Gastrointestinal bleed</p>
<p>PPI = proton pump inhibitor; SUP = stress ulcer prophylaxis.</p>	

physician progress notes during their hospitalization. In addition to physician progress notes, we reviewed patient medication profiles and active problem lists to determine which patients met criteria for inclusion in this study. We excluded patients who had received outpatient treatment with a PPI within the 8 weeks immediately prior to hospital admission, had been transferred from a critical care unit or an outside hospital, or were prescribed a PPI for an appropriate indication (Table 1).

Utilization and cost determinations

To determine inpatient PPI utilization and cost, we collected information pertaining to the specific medication prescribed for SUP, including the specific PPI ordered (for example, omeprazole), if applicable; length of therapy; prescribed dose; frequency; exact number of doses received, as ascertained through the VA’s bar code

medication administration (BCMA) system; and route of administration.

To allow other institutions to weigh the economic impact of this study, we calculated the economic cost of PPI utilization using McKesson’s 2008 average wholesale price (AWP), a benchmark for prescription drug pricing.¹⁷ We determined the inpatient cost over the course of the 3-month study by multiplying the exact number of PPI doses administered for SUP by the particular PPI’s AWP and extrapolated yearly inpatient costs by multiplying that total by 4.

After thoroughly reviewing discharge orders, progress notes, and outpatient medication profiles for all who had received a PPI for SUP while inpatients, we identified inappropriate discharge PPI prescriptions, calculating outpatient cost based on the type of PPI prescribed, AWP, and the prescribed dose and frequency multiplied by 0.5 (to account for the fact

that previous studies have found that patients prescribed self-administered medications typically take less than half of the doses dispensed).¹⁸

CDAD evaluation

To assess the association between long-term PPI use and subsequent CDAD, we evaluated the records of the following 300 patients who had been prescribed a PPI as SUP during hospitalization for evidence of new onset CDAD developing during the year following discharge: all 131 discharged with a PPI prescription as SUP and 169 selected randomly from among the 315 discharged without a PPI prescription as SUP. To identify a patient as having new onset CDAD, we required the diagnosis to be documented in the physician progress notes and confirmed by a positive enzyme-linked immunosorbent assay for *C difficile* toxins A and B.

When we identified a new onset case, we reviewed the medication profile for such potential contributing factors as antibiotic use within the 8 weeks prior to CDAD diagnosis, use of any other AST besides that prescribed during the study period, and any additional hospitalization within the 3 months preceding CDAD diagnosis. We then calculated the incidence of new onset CDAD within each of the 2 discharge groups whose records were evaluated for CDAD, noting any such potential contributing factors.

Statistical analysis

Using descriptive statistics, we determined the frequency distribution of baseline characteristics among 300 patients prescribed PPIs for SUP as inpatients and, within that group, those discharged with and without PPI prescriptions for SUP. We used Chi-square analysis to evaluate differences in categorical baseline char-

Table 2. Inpatient proton pump inhibitor utilization data

	Study period ^a	Year ^b
Number of days on PPI		
• Minimum	1	—
• Maximum	45	—
• Mean (± SD)	6.5 (± 5.2)	—
Number of patients prescribed PPI for SUP		
Total number of patients prescribed PPI	446	—
• Omeprazole 20 mg po daily	427	—
• Omeprazole 20 mg po twice daily	13	—
• Pantoprazole 40 mg IV daily	5	—
• Rabeprazole 20 mg po daily	1	—
Number of inpatient PPI doses administered		
Total number of PPI doses administered	3,066	—
• Omeprazole	3,028	—
• Pantoprazole	37	—
• Rabeprazole	1	—
Inpatient PPI utilization cost		
Average wholesale price	\$13,157	\$52,628
IV = intravenous; PPI = proton pump inhibitor; po = by mouth; SUP = stress ulcer prophylaxis. ^a Includes study period May 1, 2006, to July 31, 2006. ^b Extrapolation of data (from May 1, 2006–July 31, 2006) for 1 year.		

acteristics among patients discharged with or without a PPI prescription. To analyze the relationship between age and duration of PPI usage within the 2 discharge groups, we used the Student's *t* test. To determine whether incidence of new onset CDAD differed significantly between the 2 discharge groups, we applied Fisher's exact test. We performed all statistical analysis using SAS v9.1 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 1,557 patients were admitted to general medicine units during the 3-month study period, and 1,182 of them were prescribed a PPI during hospitalization (Figure). Of the patients given inpatient PPI treatment, 446 (37.7%) were prescribed the

PPI for SUP, and 736 (62.3%) were prescribed the PPI for an appropriate indication. At discharge, 131 (29.3%) of the patients receiving a PPI for SUP were continued on PPI therapy post-hospitalization; 315 were not.

The mean duration of inpatient PPI therapy for SUP was 6.5 days (Table 2). Most (95.7%) patients treated for SUP received the preferred formulary agent, omeprazole 20 mg by mouth (po) once daily during hospitalization, though 13 (2.9%) received omeprazole 20 mg po twice daily. The remaining 6 patients received a nonformulary agent: 5 (1.1%) received pantoprazole 40 mg intravenous (IV) daily and 1 (0.22%) received rabeprazole 20 mg po daily.

We calculated the inpatient cost of PPI therapy for SUP based on the

actual number of PPI doses administered during the 3-month study period: 3,028 doses of omeprazole, 37 doses of pantoprazole, and 1 dose of rabeprazole. Total calculated costs of omeprazole, pantoprazole, and rabeprazole were \$12,596.48, \$555.00, and \$5.67, respectively. This brought the total inpatient cost of PPI utilization for the inappropriate indication of SUP to \$13,157.15 during the study period and the extrapolated annual inpatient cost of such inappropriate PPI utilization to \$52,628.60.

Of the 131 patients given an inappropriate discharge prescription for PPI therapy, 118 (90.1%) were prescribed omeprazole 20 mg po daily (including 2 of the 5 who had received pantoprazole while inpatients), and 13 (9.9%) were prescribed omeprazole 20 mg po twice daily (all received this regimen while inpatients). Assuming an omeprazole cost per dose of \$4.16 and a 50% adherence rate, the outpatient PPI utilization cost for these 131 patients would be \$8,985.60 over a 1-month (30-day) period: \$62.40 per month or approximately \$748.80 per year for each patient prescribed omeprazole 20 mg po once daily, and \$124.80 per month or approximately \$1,497.60 per year for each patient prescribed omeprazole 20 mg po twice daily.

Among the patients whose records were evaluated for CDAD, we found no statistically significant differences in baseline characteristics between those discharged with and those discharged without PPI prescriptions for SUP (Table 3). Of the 131 patients discharged with PPI prescriptions, 96.2% were male vs 98.2% of the 169 patients discharged without PPI prescriptions. For patients discharged with and without PPI prescriptions, the mean ages were 63.7 years and 60.5 years, respectively, with the for-

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mer group ranging from 29 to 94 years and the latter ranging from 20 to 93 years. Most patients in both groups (61% in the group discharged with PPI prescriptions and 56.8% in the group discharged without PPI prescriptions) were white.

According to medication profiles, none of the patients whose records were evaluated for CDAD had used any AST, other than that which had been prescribed during the study period, within the 8 weeks preceding CDAD diagnosis, and none had any additional hospitalization within the 3 months preceding CDAD diagnosis. Patients discharged with a PPI prescription had a higher incidence of new onset CDAD within the year following discharge than did patients discharged without a PPI prescription (9.2% vs 1.8%, respectively; $P = .0057$). Between the 2 cohorts, antibiotic usage prior to CDAD diagnosis did not differ significantly.

DISCUSSION

Stress ulceration is frequent in ICUs and mortality from resultant bleeding may exceed 50%.³⁻⁵ Current literature and ASHP guidelines recommend prescribing AST, such as PPIs, for SUP in patients being treated for 1 week or more in an ICU.^{2,6-9} Many providers, however, use PPIs inappropriately in general medicine units. This study evaluated the economic and health effects of PPI utilization in a large VA medical center by following a cohort of patients from admission to a general medicine unit through 1 year following discharge. To date, only a small number of studies have evaluated the use of AST for SUP in general medicine units.

In our facility, 446 (37.7%) of the 1,182 patients who were prescribed inpatient PPI therapy over the course of 3 months did not have an appropriate indication. The cost of this un-

Table 3. Baseline characteristics of patients whose records were evaluated for new onset, community-acquired CDAD within the year following discharge

Characteristic	Discharged with PPI prescription (n = 131)	Discharged without PPI prescription (n = 169)	P value
Sex			
Male No. (%)	126 (96.2)	166 (98.2)	.2763
Female No. (%)	5 (3.8)	3 (1.8)	—
Age, y			
Mean (SD)	63.7 (± 13.1)	60.5 (± 13.3)	.8342
Range	29–94	20–93	—
Race			
White No. (%)	80 (61.0)	96 (56.8)	.4570
Black No. (%)	44 (33.6)	65 (38.5)	.3840
Hispanic No. (%)	7 (5.3)	7 (4.1)	—
Asian No. (%)	0 (0.0)	1 (0.59)	1.000
CDAD = <i>Clostridium difficile</i> -associated disease; PPI = proton pump inhibitor; SUP = stress ulcer prophylaxis.			

necessary treatment was \$13,157.15 during the study period, representing an extrapolated annual cost of \$52,628.60. Unlike previous studies, ours accurately tracked each inpatient PPI dose administered for SUP using BCMA records, permitting an exact cost calculation.

Heidelbaugh and colleagues also found a significant number of patients—389 (22%) of 1,769 over a 4-month period—received AST for SUP in non-ICU units.¹⁹ The Heidelbaugh study, however, evaluated the use of all AST, histamine-2 receptor antagonists as well as PPIs. The calculated inpatient cost of SUP therapy was thus much higher in our study over a shorter period—\$13,157.15

over 3 months vs \$11,024 over 4 months (\$33,072 annually).¹⁹ Cost differences between our studies could be attributed to different prescribing patterns at the 2 institutions.

In addition to unnecessary inpatient costs, inappropriate PPI prescription is responsible for a substantial amount of unnecessary outpatient costs. Our study found that a significant number of patients, 131 (29.3%) of 446, were discharged with PPI prescriptions though they had no indication for such therapy. Other studies have found as many as 54% of patients being discharged with a prescription for some type of AST after being treated inappropriately for SUP while in a non-ICU hospital setting.¹⁹

Table 4. Incidence of new onset, community-acquired CDAD among patients discharged with and without a proton pump inhibitor prescription

	Discharged with PPI prescription (n = 131)	Discharged without PPI prescription (n = 169)	P value
CDAD No. (%) of patients	12 (9.2)	3 (1.8)	.0057
Antibiotic usage within the 8 weeks prior to CDAD diagnosis No. (%) of patients	6 (4.6)	2 (1.2)	.0832

CDAD = *Clostridium difficile*-associated disease; PPI = proton pump inhibitor.

Study limitations and future directions

Our study is limited by its short duration. Although it provides very accurate information about prescribing patterns at our institution during the 3-month study period, we only can assume long-term practices in the outpatient and hospital setting. A 1-year study period would have been preferable. Another limitation is that we could not track actual outpatient pill counts but had to assume an outpatient adherence rate of 50%, which previous studies had found to be typical of patients prescribed self-administered medications.¹⁸ A prospective study evaluating patient adherence through monthly pill counts or a review of medication refill history would more accurately calculate outpatient PPI utilization costs. Despite these limitations, we were able to identify preventable annual costs of \$160,455.80 at our institution: at least \$107,827.20 in annual outpatient costs and \$52,628.60 in annual inpatient costs.

Because our study focused solely on PPI drug cost, we would suggest that future studies investigate the in-

direct costs associated with PPI use, such as the costs of treating complications caused by drug-drug interactions. Although our study did not focus on drug interactions, PPI treatment may diminish therapeutic effects of clopidogrel and mesalamine; decrease absorption of antiviral agents (such as atazanavir, indinavir, and nelfinavir), antineoplastic agents (such as erlotinib and dasatinib), and antifungal agents (such as ketoconazole and itraconazole); and increase serum concentrations of phenytoin, warfarin, benzodiazepines, and cimetidine.²⁰ Recently, the FDA has issued an ongoing safety review of clopidogrel and its efficacy when administered in conjunction with a PPI. In a recent retrospective cohort study of 8,205 patients with acute coronary syndrome (ACS), Ho and colleagues found the concomitant use of clopidogrel and a PPI was significantly associated with an increased risk of death from or hospitalization for ACS compared with clopidogrel alone.²¹

CDAD appears to be growing at an alarming rate, and there is increasing evidence that it may be associated with PPI therapy.²² Several studies

have found that the inappropriate prescribing and overuse of PPIs increase patients' risk of infectious diseases. In a case-controlled study, Dial and colleagues evaluated 317 cases of CDAD, defined by oral vancomycin use, and determined whether patients had been exposed to PPIs 90 days prior to initiation of treatment. Compared with a control group, the patients who had received PPIs were found to be at significantly higher risk for CDAD.²³ Likewise, Cadle and colleagues reviewed patients diagnosed with CDAD and compared cure rates among those who were receiving concurrent PPI therapy and those who were not.²⁴ Investigators found significant differences in cure rates favoring the group not receiving PPI therapy: 63% were cured of CDAD compared with 38% in the group receiving PPIs. In addition, the recurrence rate for CDAD was 4.17 times greater in patients taking a PPI compared with those who were not.²⁴

Our retrospective chart review was not designed to determine whether PPI therapy causes CDAD, though we did identify the number of patients diagnosed with new onset CDAD while receiving PPI therapy. While the overall incidence of CDAD was low, it differed significantly between patients receiving inappropriate, long-term PPI therapy and those who were not ($P = .0057$). Although antibiotic usage prior to a confirmed CDAD diagnosis did not differ significantly between the 2 groups ($P = .0832$), our study was limited in that the CPRS allowed us only to identify antibiotic use in patients treated at our institution. We could not determine whether patients received antibiotics from other facilities prior to CDAD diagnosis.

We recommend further investigation to evaluate the association between PPIs and CDAD onset. Such

research would be beneficial in determining the indirect costs of treating CDAD resulting from inappropriate use of long-term PPI therapy. Medical literature has indicated that hospital costs of treating CDAD are approximately \$4,000 per patient.^{25,26} Assuming PPI therapy was the primary cause of CDAD for the 12 patients diagnosed with that disease from among those discharged with a PPI prescription in our study, the estimated hospital costs for management would be \$48,000.

CONCLUSION

The inappropriate prescription of PPIs for SUP in general medicine units results in unnecessary inpatient and outpatient medication use and costs. The findings of this study suggest that our institution should develop SUP protocols to reduce the inappropriate prescription of PPIs and to prevent the onset of any associated CDAD.

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Author disclosures

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