Original Investigation

Histamine-2 Receptor Antagonists vs Proton Pump Inhibitors on Gastrointestinal Tract Hemorrhage and Infectious Complications in the Intensive Care Unit

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IMPORTANCE Histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) are commonly used to prevent gastrointestinal tract (GI) hemorrhage in critically ill patients. The stronger acid suppression of PPIs may reduce the rate of bleeding but enhance infectious complications, specifically pneumonia and *Clostridium difficile* infection (CDI).

OBJECTIVE To evaluate the occurrence and risk factors for GI hemorrhage, pneumonia, and CDI in critically ill patients.

DESIGN, SETTING, AND PARTICIPANTS A pharmacoepidemiological cohort study was conducted of adult patients requiring mechanical ventilation for 24 hours or more and administered either an H_2RA or PPI for 48 hours or more while intubated across 71 hospitals between January 1, 2003, and December 31, 2008. Propensity score–adjusted and propensity-matched multivariate regression models were used to control for confounders.

MAIN OUTCOMES AND MEASURES Primary outcomes were secondary diagnoses of *International Classification of Diseases, Ninth Revision* (*ICD-9*)–coded GI hemorrhage, pneumonia, and CDI occurring 48 hours or more after initiating invasive ventilation.

RESULTS Of 35 312 patients, 13 439 (38.1%) received H_2RAs and 21 873 (61.9%) received PPIs. Gastrointestinal hemorrhage (2.1% vs 5.9%; $P < .001$), pneumonia (27% vs 38.6%; $P < .001$), and CDI (2.2% vs 3.8%; $P < .001$) occurred less frequently in the H_2RA group. After adjusting for propensity score and covariates, odds ratios of GI hemorrhage (2.24; 95% CI, 1.81-2.76), pneumonia (1.2; 95% CI, 1.03-1.41), and CDI (1.29; 95% CI, 1.04-1.64) were greater with PPIs. Similar results were obtained in the propensity-matched models of 8799 patients in each cohort.

CONCLUSIONS AND RELEVANCE Proton pump inhibitors are associated with greater risks of GI hemorrhage, pneumonia, and CDI than H_2RAs in mechanically ventilated patients. Numerous other risk factors are apparent. These data warrant confirmation in comparative prospective studies.

Invited Commentary

Supplemental content at jamainternalmedicine.com

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Most critically ill patients requiring mechanical ventilation will develop endoscopic evidence of stress ulceration in the upper gastrointestinal tract (GI), of whom 10% to 25% will manifest overt signs and symptoms of GI bleeding and up to 5% will progress to clinically significant hemorrhage.[1-3] Annually in the United States, nearly 1 million hospitalizations require mechanical ventilation and are at risk for stress-related GI hemorrhage and the associated detrimental outcomes of mortality, lengthened stay, and increased costs.[3-5] Other factors contributing to GI hemorrhage are poorly defined.[1-3]

Prevention of GI bleeding with acid-suppressing agents like histamine-2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) is common practice.[1-3] On the basis of differing pharmacologic mechanisms, these 2 classes of agents may possess distinct profiles of effectiveness and complication rates. Compared with antacids, sucralfate, or placebo, H_2RAs decrease the incidence of hemorrhage.[6,7] The results of recent systematic reviews indicate that PPIs further lower bleeding rates, possibly owing to greater acid suppression.[8-10] Acid suppressants, however, are not without risks. Several epidemiologic studies conducted outside the intensive care unit (ICU) suggest that the extent of acid suppression is associated with pneumonia or *Clostridium difficile* infection (CDI).[11-17] To date, only limited data are available in critically ill patients assessing the relationship between acid suppression and these infectious complications. Like GI hemorrhage, however, these infections increase the risk of mortality, lengthen ICU stay, and contribute to health care costs.[18-24]

We conducted a large cohort study to comparatively evaluate H_2RA and PPI therapies when used in critically ill patients. Specifically, we hypothesized that the stronger acid-suppressing effects of PPIs may lessen the occurrence of GI bleeding but may increase the risk of pneumonia and CDI in adult patients requiring mechanical ventilation. We also sought to identify other risk factors associated with these outcomes.

Methods

Data Source

The Colorado Multiple Institutional Review Board provided approval to conduct the study. This was a retrospective, pharmacoepidemiologic, cohort study evaluating patient data voluntarily submitted to the Premier Perspective database (Premier Inc). Data from the Premier Perspective database is de-identified, so a waiver of informed consent and Health Insurance Portability and Accountability Act was granted. This fee-supported database contains patient characteristics and therapies; disease state classifications according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Current Procedural Terminology* (*CPT*) codes; outcomes such as length of stay, mortality, and hospital costs; and a date-stamped log of all billed items including drug dosage regimens, ventilator data, and *ICD-9* codes. Disease diagnoses and *ICD-9* codes are categorized in the database as primary (present on admission) or secondary (occurring during admission).

Data Collection

The supplementary information provides *ICD-9* codes and additional definitions for outcomes and covariates (eTables 1 and 2 in the Supplement). Patients 18 years or older, who were admitted to an ICU between January 1, 2003, to December 31, 2008, requiring invasive mechanical ventilation for 24 hours or more and administered either an H_2RA or PPI for 48 hours or more while receiving invasive ventilation, were considered. Patients were excluded if any of the following conditions were present: primary or secondary diagnosis of variceal hemorrhage; primary diagnosis of GI hemorrhage or a coded bleeding event within 24 hours of requiring invasive ventilation; administration of PPIs exceeding twice daily dosing (including infusion), octreotide, or somatostatin during the first 24 hours of invasive ventilation; or administration of both an H_2RA and PPI while in the ICU (sequential or concurrent use). Exposure to acid-suppressing medications was defined a priori as any pharmacy dispensed H_2RA or PPI within the first 48 hours of ventilation.

Outcomes

The primary outcomes evaluated were secondary diagnoses of GI hemorrhage (based on the same *ICD-9* codes that excluded the primary diagnosis of hemorrhage), pneumonia, and CDI. These codes were extracted from similar studies.[15,17,25] All outcomes occurred at least 48 hours after initiating invasive ventilation so as to provide sufficient time to develop these as nosocomial events. To ensure that these outcomes were connected to ICU exposure, all events had to occur no later than 72 hours after patients were no longer deemed "ICU status" according to billing records. Exposure to acid-suppressing therapies was censored at the occurrence of GI hemorrhage for that outcome only. Secondary outcomes included ICU and hospital length of stay, mortality, and total ICU and hospital costs.

Covariates

Covariates were included if they possibly predicted the use of acid-suppressing therapies or increased the risk of GI hemorrhage, pneumonia, or CDI (eTables 1 and 2 in the Supplement). Specifically, the following characteristics were assessed: duration of acid-suppressing therapy; length of invasive ventilation; length of ICU stay; acute hepatic injury or chronic hepatic injury; acute kidney injury or chronic kidney injury; neurologic injury including coma, embolic stroke, encephalitis, head injury, hemorrhage, and spinal cord injury; pancreatitis; major surgery or trauma; sepsis; shock or hypotension; solid organ transplant; thermal injury involving 30% or more of body surface area; coagulopathy or thrombocytopenia; *Helicobacter pylori* infection; neutropenia; inflammatory bowel disease; history of GI ulcer; corticosteroid use in general and further stratified by mean daily hydrocortisone dose greater than 250 mg or 250 mg or lower (or equivalent); parenteral nutrition for 48 hours or more while receiving invasive ventilation; antibiotic use for 48 hours or more while receiving invasive ventilation; therapeutic doses of anticoagulant agents for 48 hours or more while receiving invasive ventilation; and use of platelet inhibiting agents for

Table 1. Demographics of Adult Patients Requiring Mechanical Ventilation for 24 Hours or More and Administered Either an H_2RA or PPI for 48 Hours or More While Intubated[a]

Demographic	Group			Matched Group		
	H_2RA (n = 13 439)	PPI (n = 21 873)	*P* Value[b]	H_2RA (n = 8799)	PPI (n = 8799)	*P* Value[b]
Age, y						
18-19	148 (1.1)	102 (0.5)	<.001	71 (0.8)	62 (0.7)	NS
20-29	732 (5.4)	645 (2.9)		390 (4.4)	352 (4.0)	
30-39	833 (6.2)	1010 (4.6)		464 (5.3)	507 (5.8)	
40-49	1576 (11.7)	2232 (1.2)		973 (11.1)	949 (10.8)	
50-59	2445 (18.2)	3940 (18.0)		1586 (18.0)	1589 (18.1)	
60-69	2892 (21.5)	4884 (22.3)		1888 (21.5)	1928 (21.9)	
70-79	2961 (22.0)	5305 (24.3)		2076 (23.6)	2050 (23.3)	
≥80	1852 (13.8)	3755 (17.2)		1351 (15.4)	1362 (15.5)	
Male sex	7872 (58.6)	11 899 (54.4)	<.001	4874 (55.4)	4836 (55.0)	NS
Race						
White	10 212 (76.0)	15 708 (71.8)	<.001	6636 (75.4)	6357 (72.2)	<.001
Black	2220 (16.5)	4902 (22.4)		1523 (17.3)	1916 (21.8)	
Hispanic	347 (2.6)	262 (1.2)		228 (2.6)	124 (1.4)	
Other	660 (4.9)	1001 (4.6)		412 (4.7)	402 (4.8)	
Primary insurance						
Medicare	6927 (51.5)	12 961 (59.3)	<.001	4837 (55.0)	4928 (56.0)	<.001
Medicaid	1762 (13.1)	2501 (11.4)		1175 (13.4)	1044 (11.9)	
Private	3328 (24.8)	4306 (19.7)		1995 (22.7)	1846 (21.0)	
Self-pay/other	1422 (10.6)	2105 (9.6)		792 (9.0)	981 (11.1)	
Admission year						
2003	3729 (27.8)	2704 (12.4)	<.001	1719 (19.5)	1715 (19.5)	NS
2004	2804 (20.9)	3542 (16.2)		1631 (18.5)	1767 (20.1)	
2005	2223 (16.5)	3913 (17.9)		1614 (18.3)	1552 (17.6)	
2006	2231 (16.6)	4086 (18.7)		1696 (19.3)	1606 (18.3)	
2007	1558 (11.6)	4366 (20)		1324 (15)	1349 (15.3)	
2008	894 (6.7)	3262 (14.9)		815 (9.3)	810 (9.2)	
Case-mix index, mean (SD)	1.47 (0.1)	1.46 (0.1)	NS	1.49 (0.1)	1.48 (0.1)	NS

Abbreviations: H_2RA, histamine-2 receptor antagonist; NS, not significant ($P > .05$); PPI, proton pump inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise specified.

[b] *P* values compare H_2RA and PPI groups via the χ^2 test or unpaired *t* test.

48 hours or more while receiving invasive ventilation. Demographics included age, sex, race, payer status, most common primary diagnoses, and most common secondary diagnoses. The number of beds, geographical location, teaching status, and service of an urban or rural patient population was documented for each hospital. Patients participated in the assessment once per hospital admission and the primary outcomes were only assessed for the initial ICU admission. A dichotomous dose effect of acid suppressants was analyzed according to the mean daily dose while receiving mechanical ventilation, with high daily dose defined for H_2RAs as greater than 40 mg for famotidine, greater than 150 mg for ranitidine hydrochloride if intravenous or greater than 300 mg if enteral, greater than 300 mg for nizatidine, or greater than 1200 mg for cimetidine and defined for PPIs as greater than 40 mg for omeprazole magnesium or sodium, esomeprazole magnesium or sodium, or pantoprazole sodium or greater than 30 mg for lansoprazole.

Data Analysis

Patients receiving H_2RAs for the prevention of GI hemorrhage may differ from those receiving PPIs. To address confounding by indication, a propensity score was determined using a multivariate generalized estimating equation (GEE) with a logit-link (SAS PROC GENMOD), where the use of H_2RAs or PPIs was the dependent variable and the covariates of age, sex, admission year, primary diagnosis, *ICD-9*-coded disease states occurring within 48 hours of admission to the ICU, and use of corticosteroids, anticoagulants, platelet inhibitors, or total parenteral nutrition within 48 hours of admission to the ICU were the independent variables. The model accounted for clustering of admissions within hospitals and year of admission. The fitted probability from this model was applied as the propensity score by assigning it to each admission in an effort to delineate the propensity to receive H_2RAs or PPIs. The *c* statistic for the propensity score was 0.81, indicating a good ability to discriminate between admissions receiving H_2RAs or PPIs. In

Table 2. Patient Illness Characteristics[a]

Illness Characteristic	Group			Matched Group		
	H_2RA (n = 13 439)	PPI (n = 21 873)	*P* Value[b]	H_2RA (n = 8799)	PPI (n = 8799)	*P* Value[b]
Primary diagnoses (most common)						
Coronary artery disease	2464 (18.3)	1778 (8.1)	<.001	1178 (13.4)	902 (10.3)	NS
Acute respiratory failure	1987 (14.8)	4947 (22.6)		1637 (18.6)	1701 (19.3)	
Myocardial infarction	673 (5.0)	882 (4.0)		378 (4.3)	383 (4.4)	
Chest pain, unspecified	631 (4.7)	NA		331 (3.8)	NA	
Sepsis	524 (3.9)	1737 (7.9)		467 (5.3)	436 (5)	
Congestive heart failure	423 (3.1)	857 (3.9)		292 (3.3)	338 (3.8)	
Pneumonia	369 (2.7)	1071 (4.9)		305 (3.5)	338 (3.8)	
Intracerebral hemorrhage	362 (2.7)	540 (2.5)		257 (2.9)	236 (2.7)	
Aortic valve disorder	348 (2.6)	NA		219 (2.5)	NA	
Acute on chronic respiratory failure	318 (2.4)	559 (2.6)		255 (2.9)	236 (2.7)	
Shortness of breath, unspecified	NA	767 (3.5)		NA	250 (2.8)	
Pneumonitis	NA	512 (2.3)		NA	194 (2.2)	
Secondary diagnoses (most common)						
Hypertension	5823 (43.3)	8298 (37.9)	<.001	3721 (42.3)	3555 (40.4)	NS
Acute respiratory failure	4113 (30.6)	9837 (45)		3308 (37.6)	3164 (36)	
Congestive heart failure	2913 (21.7)	6808 (31.1)		2139 (24.3)	2488 (28.3)	
Atrial fibrillation	2726 (20.3)	5426 (24.8)		1898 (21.6)	2004 (22.8)	
Diabetes	2521 (18.8)	4358 (19.9)		1665 (18.9)	1714 (19.5)	
Tobacco use disorder	2379 (17.7)	3388 (15.5)		1513 (17.2)	1387 (15.8)	
Coronary artery disease	2314 (17.2)	3876 (17.7)		1437 (16.3)	1603 (18.2)	
Chronic obstructive airway disease	2223 (16.5)	3972 (18.2)		1555 (17.7)	1514 (17.2)	
Hyperlipidemia	2208 (16.4)	3753 (17.2)		1416 (16.1)	1506 (17.1)	
Anemia	2137 (15.9)	3865 (17.7)		1522 (17.3)	1507 (17.1)	
Hypokalemia	1999 (14.9)	4195 (19.2)		1459 (16.6)	1581 (18.0)	
Respiratory failure following trauma or surgery	1937 (14.4)	2001 (9.2)		1171 (13.3)	1263 (14.4)	
Acidosis	1859 (13.8)	4094 (18.7)		1396 (15.9)	1332 (15.1)	
Pulmonary collapse	1648 (12.3)	2805 (12.8)		1057 (12.0)	1142 (13.0)	
Pneumonia	1644 (12.2)	3713 (17.0)		1289 (14.6)	1280 (14.3)	
Acute kidney injury	1639 (12.2)	4871 (22.3)		1394 (15.8)	1404 (16.0)	
Urinary tract infection	1590 (11.8)	3813 (17.4)		1252 (14.2)	1270 (14.4)	
Systemic inflammatory response syndrome	1201 (9.0)	3201 (14.6)		876 (10.0)	880 (10.0)	
Pneumonitis	1105 (8.2)	3005 (13.7)		1021 (11.6)	1102 (12.5)	
Protein deficiency	1051 (7.8)	2949 (13.5)		904 (10.3)	1055 (12.0)	

(continued)

addition to acid suppression groups and the aforementioned covariates, the propensity score was included as an independent variable in the final GEE regression models against the dependent variables of GI hemorrhage, pneumonia, and CDI. Model calibration was assessed using the Hosmer-Lemeshow test statistic. To assess the effect of misclassification across covariates and outcomes, probabilistic sensitivity analyses were conducted by varying all parameters within a model by ±25% using a second-order Monte Carlo simulation with 1000 repetitions and determining the likelihood that an odds ratio would no longer be significant.

Cohort matching was then conducted based on the propensity score for groups receiving H_2RAs vs PPIs using a greedy matching technique with the algorithm searching for 1:1 matches at a tolerance of 0.0005.[26,27] Additional GEE regression models were completed using the same independent covariates as the aforementioned models to determine parameters associated with GI hemorrhage, pneumonia, and CDI.

Data are presented as frequencies and proportions for categorical data or means, medians, and interquartile ranges for continuous variables. Unadjusted incidence rates of GI hemorrhage, pneumonia, and CDI were compared between H_2RA and PPI groups using χ^2 test. Patient and hospital characteristics were compared between groups using the χ^2 test for categorical data and the unpaired *t* test, Kruskal-Wallis test, or Mann-Whitney test for continuous variables. A 2-sided *P* value <.05 was considered statistically significant. The GEE models yielded odds ratios and 95% confidence intervals. All univariate and multivariate analyses were conducted using SAS version 9.3 (SAS Institute Inc). Monte Carlo analyses were completed using a macro function in Excel 2010 (Microsoft Corp).

Table 2. Patient Illness Characteristics[a] (continued)

Illness Characteristic	Group			Matched Group		
	H_2RA (n = 13 439)	PPI (n = 21 873)	*P* Value[b]	H_2RA (n = 8799)	PPI (n = 8799)	*P* Value[b]
Predefined *ICD-9* codes						
Sepsis	3315 (24.7)	8589 (39.3)	<.001	2676 (30.4)	2761 (31.4)	NS
Shock/hypotension	2736 (20.4)	6821 (31.2)	<.001	2166 (24.6)	2174 (24.7)	NS
Kidney injury	2811 (20.9)	8308 (38.0)	<.001	2400 (27.3)	2470 (28.1)	NS
Acute	2613 (19.4)	7586 (34.7)	<.001	2204 (25.0)	2243 (25.5)	NS
Chronic	697 (5.2)	2728 (12.5)	<.001	699 (7.9)	721 (8.2)	NS
Neurologic injury	2799 (20.8)	4109 (18.8)	<.001	1712 (19.5)	1735 (19.7)	NS
Thrombocytopenia	923 (6.9)	2702 (12.4)	<.001	757 (8.6)	830 (9.4)	NS
Hepatic injury	392 (2.9)	1281 (5.9)	<.001	349 (4.0)	376 (4.3)	NS
Acute	158 (1.2)	614 (2.8)	<.001	148 (1.7)	150 (1.7)	NS
Chronic	250 (1.9)	751 (3.4)	<.001	220 (2.5)	247 (2.8)	NS
Surgery/trauma	1820 (13.5)	1421 (6.5)	<.001	862 (9.8)	855 (9.7)	NS
Coagulopathy	438 (3.3)	1211 (5.5)	<.001	343 (3.9)	377 (4.3)	NS
Pancreatitis	299 (2.2)	652 (3.0)	<.001	238 (2.7)	256 (2.9)	NS
Gastrointestinal ulcer	182 (1.4)	626 (2.9)	<.001	230 (2.6)	242 (2.8)	NS
Inflammatory bowel disease	136 (1.0)	228 (1.0)	NS	98 (1.1)	86 (1.0)	NS
Burns	141 (1.0)	21 (0.1)	NS	111 (1.3)	108 (1.2)	NS
Neutropenia	41 (0.3)	146 (0.7)	<.001	32 (0.4)	54 (0.6)	NS
Helicobacter pylori	16 (0.1)	26 (0.1)	NS	10 (0.1)	12 (0.1)	NS
Solid organ transplant	6 (0.0)	9 (0.0)	NS	5 (0.1)	4 (0.0)	NS
Predefined drug therapies						
Antibiotic	10 119 (75.3)	18 298 (83.7)	<.001	6803 (77.3)	7145 (81.2)	<.001
Ampicillin ± sulbacatam	759 (5.6)	1407 (6.4)	NS	506 (5.8)	600 (6.8)	NS
Piperacillin ± tazobactam	2856 (21.3)	7134 (32.6)	<.001	2160 (24.5)	2551 (29.0)	<.001
Carbapenem	1087 (8.1)	3226 (14.7)	<.001	829 (9.4)	1049 (11.9)	<.001
Clindamycin	1000 (7.4)	1983 (9.1)	.01	696 (7.9)	816 (9.3)	.02
Third-fourth-generation cephalosporin	6749 (50.2)	10 077 (46.1)	<.001	4260 (48.4)	4097 (46.6)	<.001
Fluoroquinolone	3343 (24.9)	8401 (38.4)	<.001	2502 (28.4)	3040 (34.5)	<.001
Corticosteroid use	4483 (33.4)	8910 (40.7)	<.001	3241 (36.8)	3239 (36.8)	NS
>250-mg Hydrocortisone equivalent per day	3268 (72.9)	6937 (77.9)	<.001	2554 (78.8)	2548 (78.7)	NS
Anticoagulants	4575 (34.0)	7389 (33.8)	NS	3208 (36.5)	2737 (31.1)	<.001
Platelet inhibitors	4417 (32.9)	7260 (33.2)	NS	2713 (30.8)	2938 (33.4)	<.001
Parenteral nutrition	14 (0.1)	55 (0.3)	.002	11 (0.1)	19 (0.2)	NS

Abbreviations: H_2RA, histamine-2 receptor antagonist; *ICD-9*, *International Classification of Diseases, Ninth Revision*; NA, not applicable; NS, not significant; PPI, proton pump inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise specified. Definitions of disease states and drug therapies are provided in the eAppendix in the Supplement.

[b] *P* values compare H_2RA and PPI groups via the χ^2 test.

Results

Univariate Analyses

The study period included 41 211 patients requiring mechanical ventilation. Of these, 6004 did not meet inclusion criteria: 4811 received both an H_2RA and PPI, 624 presented with a primary or secondary diagnosis of variceal hemorrhage or received octreotide or somatostatin, 293 required less than 24 hours of invasive ventilation, 224 presented with a primary diagnosis of GI hemorrhage, and 52 received PPIs exceeding twice daily dosing. A total of 35 312 patients from 71 hospitals were included in the analysis, 13 439 (38.1%) in the H_2RA group and 21 873 (61.9%) in the PPI group (**Table 1**). The predominant primary diagnoses were coronary artery disease and/or myocardial infarction and acute respiratory failure, and the most common secondary diagnoses were hypertension, acute respiratory failure, congestive heart failure, and atrial fibrillation (**Table 2**). Only 12.3% of patients were previously admitted to the hospital within 12 months of study inclusion. Institutions were most commonly represented by urban, nonteaching hospitals with 300 to 500 beds located in the southern region of the United States (**Table 3**).

Famotidine was the most common H_2RA prescribed, and 12.7% of patients receiving H_2RAs received high-dose administration. Pantoprazole was the most common PPI pre-

Table 3. Hospital Characteristics[a]

Hospital Characteristic	Group		P Value[b]	Matched Group		P Value[b]
	H_2RA (n = 13 439)	PPI (n = 21 873)		H_2RA (n = 8799)	PPI Group (n = 8799)	
No. of beds						
<200	819 (6.1)	1612 (7.4)	<.001	553 (6.3)	635 (7.2)	<.001
200-300	2176 (16.2)	4364 (20)		1541 (17.5)	1917 (21.8)	
301-400	4064 (30.2)	6702 (30.6)		2403 (27.3)	2699 (30.7)	
401-500	1871 (13.9)	4005 (18.3)		1265 (14.4)	1576 (17.9)	
>500	4529 (33.7)	5224 (23.9)		3055 (34.7)	1980 (22.5)	
Location						
Urban	10 200 (75.9)	18 305 (83.7)	<.001	6941 (78.9)	7269 (82.6)	<.001
Rural	3239 (24.1)	3568 (16.3)		1858 (21.1)	1530 (17.4)	
Region						
South	8203 (61)	13 676 (62.5)	<.001	5174 (58.8)	5519 (62.7)	<.001
Midwest	2325 (17.3)	2253 (10.3)		1482 (16.8)	873 (9.9)	
Northeast	2219 (16.5)	4752 (21.7)		1634 (18.6)	1995 (22.7)	
West	692 (5.1)	1192 (5.4)		509 (5.8)	412 (4.7)	
Teaching status						
Nonteaching	7295 (54.3)	11 181 (51.1)	<.001	4552 (51.7)	4729 (53.7)	.008
Teaching	6144 (45.7)	10 692 (48.9)		4247 (48.3)	4070 (46.3)	

Abbreviations: H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

[a] Data are presented as number (percentage) of hospitals unless otherwise specified.

[b] *P* values compare H_2RA and PPI groups via the χ^2 test.

Table 4. Acid-Suppressing Therapies[a]

Therapy Characteristic	Group		P Value[b]	Matched Group		P Value[b]
	H_2RA (n = 13 439)	PPI (n = 21 873)		H_2RA (n = 8799)	PPI (n = 8799)	
Agent[c]						
Famotidine	11 617 (86.4)	0	NA	7679 (87.3)	0	NA
Ranitidine	2535 (18.9)	0		1591 (18.1)	0	
Cimetidine	26 (0.2)	0		19 (0.2)	0	
Pantoprazole	0	16 330 (74.7)		0	6772 (77)	
Lansoprazole	0	4998 (22.9)		0	1865 (21.2)	
Esomeprazole	0	2618 (12)		0	864 (9.8)	
Omeprazole	0	381 (1.7)		0	125 (1.4)	
High dose	1707 (12.7)	10 282 (47)	<.001	967 (11)	4043 (45.9)	<.001
Duration of therapy						
<72 h	8751 (65.1)	11 212 (51.3)	<.001	5399 (61.4)	4957 (56.3)	<.001
3 to 7 d	2978 (22.2)	6457 (29.5)		2136 (24.3)	2372 (27)	
8 to 14 d	1186 (8.8)	2570 (11.7)		885 (10.1)	915 (10.4)	
>14 d	524 (3.9)	1634 (7.5)		379 (4.3)	555 (6.3)	
Duration of mechanical ventilation						
<72 h	7815 (58.2)	9775 (44.7)	<.001	4767 (54.2)	4379 (49.8)	<.001
3 to 7 d	3331 (24.8)	7028 (32.1)		2381 (27.1)	2607 (29.6)	
8 to 14 d	1461 (10.9)	2960 (13.5)		1056 (12)	1070 (12.2)	
>14 d	832 (6.2)	2110 (9.6)		595 (6.8)	743 (8.4)	

Abbreviations: H_2RA, histamine-2 receptor antagonist; NA, not applicable; PPI, proton pump inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise specified.

[b] *P* values compare H_2RA and PPI groups via the χ^2 test.

[c] More than one agent from the same acid suppressing drug class may have been administered to the same subject on different days of the ICU stay.

scribed, and 47% of patients receiving PPIs received high-dose administration (98.9% of high dose was twice daily dosing). Groups were statistically different with respect to baseline demographics (Table 1), primary and secondary

Table 5. Primary and Secondary Outcomes[a]

Outcome	Group			Matched Group		
	H_2RA (n = 13 439)	PPI (n = 21 873)	*P* Value[b]	H_2RA (n = 8799)	PPI (n = 8799)	*P* Value[b]
Primary outcomes						
GI hemorrhage	276 (2.1)	1287 (5.9)	<.001	209 (2.4)	415 (4.7)	<.001
Pneumonia	3630 (27)	8435 (38.6)	<.001	2705 (30.7)	2992 (34)	<.001
Clostridium difficile infection	294 (2.2)	835 (3.8)	<.001	227 (2.6)	300 (3.4)	.002
Secondary outcomes						
ICU length of stay, median (IQR), d	4 (2-9)	5 (1-11)	.002	4 (2-9)	5 (2-10)	.01
Hospital length of stay, median (IQR), d	6 (3-10)	6 (3-11)	NS	6 (3-10)	6 (3-11)	NS
ICU mortality, No. (%)	1449 (10.8)	3901 (17.8)	<.001	1081 (12.3)	1345 (15.3)	<.001
Hospital mortality after ICU, No. (%)	684 (5.1)	1705 (7.8)	<.001	526 (6)	582 (6.6)	.09
ICU costs, median (IQR), $	17 076 (10 747-29 215)	18 946 (10 753-35 769)	.001	17 723 (10 477-31 180)	17 692 (10 379-32 504)	NS
Hospital costs after ICU, median (IQR), $	5952 (2451-12 392)	6282 (2376-14 043)	.02	6120 (2385-13 296)	6112 (2373-13 066)	NS

Abbreviations: GI, gastrointestinal tract; H_2RA, histamine-2 receptor antagonist; ICU, intensive care unit; IQR, interquartile range; NS, not significant; PPI, proton pump inhibitor.

[a] Data are presented as number (percentage) of patients or median (IQRs).

[b] *P* values compare H_2RA and PPI groups via the χ^2 test or Mann-Whitney test.

diagnoses (Table 2), predefined *ICD-9* codes (Table 2), predefined drug therapies (Table 2), and the hospital characteristics they represented (Table 3). The duration of therapy reflected the duration of mechanical ventilation, with most of the patients receiving H_2RAs or PPIs for 7 days or less, most commonly for 3 days or less (**Table 4**).

The unadjusted rates of GI hemorrhage, pneumonia, and CDI were higher in the PPI group (**Table 5**). The secondary outcomes of ICU length of stay, mortality, and ICU and hospital costs were all greater in the PPI group (Table 5).

Multivariate Analyses

After adjusting for differences in patient characteristics, admission year, comorbidities and drug therapies, type and duration of acid-suppressing therapies, hospital characteristics, and propensity scores, odds ratios of developing a secondary GI hemorrhage, pneumonia, and CDI while in the ICU were greater in the PPI group compared with the H_2RA group (**Table 6**). Dose and duration of acid-suppressing therapy did not affect these outcomes. The duration of invasive ventilation was associated with pneumonia and CDI (Table 6). Other variables associated with GI hemorrhage were age 50 years or older, male sex, acute respiratory failure, sepsis, shock, acute kidney injury, acute or chronic hepatic injury, neurologic injury, myocardial infarction, and coagulopathy (Table 6). Conversely, thrombocytopenia, hypertension, and the use of platelet inhibitors were associated with lower risks of hemorrhage (Table 6). Other independent risk factors for pneumonia were male sex, acute respiratory failure, sepsis, acute and chronic kidney injury, acute hepatic injury, neurologic injury, trauma, transplant, congestive heart failure, myocardial infarction, and parenteral nutrition (Table 6). Black race, advanced age, hypertension, and coronary artery disease were associated with lower pneumonia risks (Table 6). Other parameters associated with CDI were acute respiratory failure, acute and chronic kidney disease, acute hepatic injury, congestive heart failure, trauma, transplant, inflammatory bowel disease, and the use of carbapenems, piperacillin, or parenteral nutrition (Table 6). Hypertension was associated with a lower CDI risk (Table 6).

Probabilistic Sensitivity Analyses

Monte Carlo probabilistic analyses showed that random variance in the classification of outcomes and covariates would produce nonsignificant odds ratios in less than 1% of all simulations for all risk factors in the multivariate models except the following: neurologic injury and GI hemorrhage (6.8% likelihood), chronic kidney injury and pneumonia (6.4% likelihood), myocardial infarction and pneumonia (5.9% likelihood), and hypertension and CDI (4.8% likelihood).

Propensity-Matched Analyses

Propensity matching resulted in 8799 patients in each group with similar baseline characteristics (Tables 1, 2, 3, and 4). After matching, the rates of GI hemorrhage, pneumonia, and CDI remained higher in the PPI group, but the only secondary outcome to display a difference was ICU mortality favoring H_2RAs (Table 5). Multivariate analyses of the matched groups showed GI hemorrhage, pneumonia, and CDI were greater in the PPI group compared with the H_2RA group (Table 6). Other covariates associated with the development of GI hemorrhage were similar to the previous model except for male sex, acute hepatic injury, sepsis, and platelet inhibitors, which lost a significant association, and congestive heart failure and parenteral nutrition, which gained a significant relationship. For pneumonia, only chronic kidney injury lost a significant association, whereas burn injury and shock gained a significant relationship (Table 6). For CDI, acute hepatic injury,

Table 6. Multivariable Regression Models of Adjusted ORs for Secondary GI Hemorrhage, Pneumonia, and CDI With Propensity Score as a Covariate and After Matching[a]

Parameter	OR (95% CI)					
	GI Hemorrhage		Pneumonia		CDI	
	Propensity Score (n = 1563)	Matching (n = 624)	Propensity Score (n = 12 065)	Matching (n = 5697)	Propensity Score (n = 1129)	Matching (n = 527)
PPI vs H_2RA, all years	2.24 (1.81-2.76)	1.95 (1.44-2.65)	1.2 (1.03-1.41)	1.23 (1.07-1.43)	1.29 (1.04-1.59)	1.31 (1.04-1.64)
2003	1.82 (1.41-2.36)	1.79 (1.27-2.53)	1.05 (0.83-1.33)	1.11 (0.89-1.40)	1.13 (0.88-1.48)	1.38 (0.90-2.13)
2004	1.81 (1.30-2.52)	1.60 (1.04-2.47)	1.09 (0.83-1.43)	1.09 (0.83-1.43)	1.08 (0.78-1.51)	1.24 (0.80-1.93)
2005	3.71 (2.67-5.16)	3.58 (2.24-5.71)	1.22 (1.00-1.48)	1.29 (1.06-1.58)	1.31 (0.95-1.81)	1.32 (0.91-1.91)
2006	2.20 (1.41-3.44)	1.51 (0.95-2.39)	1.28 (1.05-1.56)	1.36 (1.07-1.72)	1.51 (1.08-2.13)	1.53 (1.02-2.31)
2007	2.71 (1.73-4.23)	2.31 (1.31-4.07)	1.30 (1.00-1.70)	1.26 (0.93-1.69)	1.30 (0.92-1.84)	1.23 (0.82-1.85)
2008	1.71 (1.29-2.28)	1.54 (0.80-2.97)	1.32 (1.07-1.63)	1.33 (1.00-1.75)	1.43 (0.87-2.35)	1.16 (0.74-1.82)
Dose vs low-dose H_2RA						
High-dose H_2RA	0.96 (0.67-1.37)	0.95 (0.61-1.47)	1.05 (0.84-1.32)	1.00 (0.85-1.19)	0.95 (0.75-1.20)	0.92 (0.63-1.34)
Low-dose PPI	2.21 (1.98-2.44)	1.28 (1.03-1.59)	1.27 (1.12-1.44)	1.33 (1.15-1.54)	1.29 (1.06-1.55)	1.28 (1.02-1.61)
High-dose PPI	2.29 (1.76-2.82)	2.81 (2.23-3.54)	1.20 (1.07-1.35)	1.15 (1.00-1.31)	1.22 (0.95-1.56)	1.23 (0.92-1.63)
Duration of acid suppressing therapy vs <72 h						
3-7 d	1.13 (0.88-1.45)	1.12 (0.81-1.51)	1.22 (1.08-1.38)	1.17 (0.94-1.44)	0.90 (0.73-1.11)	1.08 (0.79-1.46)
8-14 d	1.30 (0.93-1.82)	1.04 (0.68-1.61)	1.34 (0.97-1.86)	1.26 (0.94-1.69)	0.77 (0.53-1.12)	0.70 (0.44-1.10)
>14 d	1.10 (0.74-1.63)	0.83 (0.43-1.59)	1.08 (0.70-1.68)	1.04 (0.80-1.36)	1.12 (0.67-1.88)	1.21 (0.77-1.89)
Age vs <40 y						
40-49	1.20 (0.88-1.62)	1.20 (0.80-1.81)	0.91 (0.80-1.04)	0.95 (0.76-1.18)	0.81 (0.54-1.21)	1.13 (0.75-1.72)
50-59	1.46 (1.18-1.83)	1.47 (1.08-1.99)	0.78 (0.66-0.92)	0.88 (0.74-1.05)	0.85 (0.62-1.16)	1.31 (0.82-2.09)
60-69	1.66 (1.26-2.19)	1.84 (1.32-2.56)	0.70 (0.58-0.84)	0.86 (0.68-1.09)	0.81 (0.56-1.17)	1.49 (0.93-2.39)
70-79	1.72 (1.27-2.34)	1.54 (0.97-2.43)	0.78 (0.65-0.94)	1.03 (0.83-1.27)	0.91 (0.61-1.36)	1.88 (1.12-3.18)
≥80	2.04 (1.48-2.83)	1.81 (1.01-3.26)	0.87 (0.71-1.06)	1.12 (0.89-1.41)	0.85 (0.56-1.28)	1.90 (1.20-2.99)
Male	1.17 (1.03-1.33)	1.04 (0.87-1.23)	1.40 (1.29-1.51)	1.33 (1.22-1.46)	1.08 (0.98-1.20)	1.06 (0.91-1.22)
Race vs white						
Black	1.14 (0.98-1.32)	1.09 (0.86-1.39)	0.81 (0.73-0.89)	0.78 (0.69-0.87)	0.85 (0.71-1.02)	0.93 (0.73-1.18)
Hispanic	1.07 (0.76-1.51)	1.20 (0.74-1.97)	1.03 (0.83-1.28)	1.07 (0.83-1.38)	0.90 (0.52-1.57)	1.18 (0.62-2.26)
Other	0.34 (0.10-1.15)	0.72 (0.43-1.22)	1.14 (0.86-1.53)	0.90 (0.71-1.12)	1.32 (0.55-3.18)	1.28 (0.76-2.16)
Mechanical ventilation days vs <72 h						
3-7 d	0.99 (0.80-1.24)	1.12 (0.80-1.57)	1.69 (1.40-2.04)	1.83 (1.43-2.33)	1.39 (1.01-1.90)	1.32 (0.88-1.98)
8-14 d	0.81 (0.61-1.07)	1.06 (0.74-1.51)	2.72 (1.87-3.94)	3.35 (2.45-4.58)	1.99 (1.20-3.29)	2.48 (1.36-4.53)
>14 d	1.06 (0.74-1.51)	1.66 (0.94-2.94)	4.17 (2.61-6.66)	5.00 (3.73-6.72)	2.07 (1.08-3.98)	1.95 (1.06-3.58)
ICD-9 coded disease state						
Acute hepatic injury	1.56 (1.29-1.88)	1.42 (0.88-2.28)	1.47 (1.23-1.73)	1.32 (1.00-1.63)	1.76 (1.25-2.49)	0.73 (0.41-1.30)
Chronic hepatic injury	1.85 (1.47-2.33)	2.36 (1.59-3.48)	0.97 (0.80-1.17)	0.92 (0.72-1.18)	0.78 (0.58-1.06)	0.98 (0.57-1.66)
Acute kidney injury	1.21 (1.02-1.43)	1.53 (1.13-2.09)	1.47 (1.30-1.66)	1.20 (1.05-1.38)	1.36 (1.04-1.77)	1.28 (1.00-1.65)
Chronic kidney injury	0.96 (0.80-1.14)	0.96 (0.70-1.31)	1.14 (1.00-1.29)	0.89 (0.74-1.06)	1.29 (1.08-1.53)	1.19 (0.88-1.62)
Burn injury	1.11 (0.80-1.41)	1.22 (0.85-1.59)	0.89 (0.41-1.93)	1.85 (1.36-2.49)	1.08 (0.81-1.33)	1.03 (0.62-1.49)
Neurologic injury	1.15 (1.00-1.32)	1.25 (1.06-1.48)	1.50 (1.35-1.67)	1.48 (1.32-1.66)	0.98 (0.84-1.14)	0.82 (0.65-1.04)
Trauma/major surgery	1.12 (0.71-1.75)	1.01 (0.63-1.73)	1.47 (1.19-1.82)	1.21 (1.04-1.41)	1.76 (1.18-2.60)	0.86 (0.54-1.37)
Transplant	1.74 (0.63-4.79)	1.18 (0.78-1.74)	2.24 (1.11-4.52)	3.96 (1.69-9.28)	5.41 (1.76-16.62)	5.26 (1.27-21.76)
Pancreatitis	1.28 (0.96-1.72)	1.42 (0.95-2.13)	1.05 (0.84-1.31)	0.94 (0.73-1.21)	1.44 (0.99-2.08)	1.29 (0.74-2.25)
Inflammatory bowel disease	1.24 (0.68-2.25)	1.29 (0.51-3.26)	Not included	Not included	3.14 (2.23-4.40)	3.57 (2.12-5.79)
Previous ulcer	0.87 (0.60-1.26)	1.14 (0.66-1.96)	Not included	Not included	0.72 (0.48-1.10)	0.80 (0.38-1.68)
Sepsis	1.00 (0.79-1.25)	1.12 (0.91-1.38)	1.28 (1.05-1.51)	1.39 (1.16-1.61)	1.43 (1.07-1.87)	1.55 (1.30-1.85)
Shock or hypotension	1.17 (1.04-1.33)	1.17 (1.00-1.34)	1.28 (1.18-1.37)	1.15 (1.02-1.30)	1.09 (0.93-1.27)	1.24 (1.04-1.49)
Coagulopathy	1.7 (1.35-2.14)	2.15 (1.51-3.05)	Not included	Not included	Not included	Not included
Neutropenia	0.68 (0.40-1.15)	0.61 (0.20-1.89)	0.77 (0.52-1.14)	1.31 (0.74-2.32)	1.08 (0.48-2.43)	1.67 (0.62-4.47)
Thrombocytopenia	0.70 (0.56-0.87)	0.65 (0.42-1.00)	Not included	Not included	Not included	Not included

(continued)

Table 6. Multivariable Regression Models of Adjusted ORs for Secondary GI Hemorrhage, Pneumonia, and CDI With Propensity Score as a Covariate and After Matching[a] (continued)

Parameter	OR (95% CI)					
	GI Hemorrhage		Pneumonia		CDI	
	Propensity Score (n = 1563)	Matching (n = 624)	Propensity Score (n = 12 065)	Matching (n = 5697)	Propensity Score (n = 1129)	Matching (n = 527)
Primary or secondary diagnosis						
Hypertension	0.77 (0.67-0.87)	0.75 (0.62-0.91)	0.79 (0.72-0.87)	0.77 (0.69-0.86)	0.87 (0.75-1.00)	0.91 (0.78-1.07)
Sepsis	1.19 (1.06-1.34)	1.12 (0.90-1.39)	1.33 (1.25-1.45)	1.44 (1.25-1.65)	1.05 (0.89-1.23)	1.55 (1.30-1.85)
Acute respiratory failure	1.24 (1.08-1.41)	1.33 (1.13-1.57)	1.50 (1.33-1.70)	2 (1.72-2.34)	2.10 (1.52-2.89)	1.14 (0.95-1.36)
Congestive heart failure	1.09 (0.96-1.25)	1.31 (1.10-1.56)	1.11 (1.02-1.20)	1.13 (1.02-1.24)	1.16 (1.04-1.29)	1.13 (0.93-1.26)
Acute kidney injury	1.19 (1.04-1.36)	0.98 (0.78-1.23)	1.24 (1.09-1.41)	1.24 (1.05-1.46)	1.09 (0.90-1.31)	1.13 (0.93-1.26)
Coronary artery disease	0.89 (0.73-1.10)	0.7 (0.51-1.16)	0.78 (0.69-0.87)	0.72 (0.62-0.85)	1.04 (0.91-1.18)	0.77 (0.61-0.99)
Myocardial infarction	1.67 (1.42-1.96)	1.68 (1.29-2.17)	1.12 (1.00-1.25)	1.21 (1.02-1.43)	0.89 (0.68-1.16)	0.94 (0.69-1.29)
Anticoagulant use	0.93 (0.79-1.10)	0.93 (0.77-1.13)	Not included	Not included	Not included	Not included
Platelet inhibitor use	0.76 (0.68-0.85)	1.04 (0.85-1.29)	Not included	Not included	Not included	Not included
Ampicillin use	Not included	Not included	Not included	Not included	1.11 (0.90-1.35)	1.26 (1.01-1.57)
Carbapenem use	Not included	Not included	Not included	Not included	1.66 (1.42-1.95)	1.56 (1.17-2.09)
Piperacillin use	Not included	Not included	Not included	Not included	1.29 (1.11-1.50)	1.27 (1.04-1.56)
Total parenteral nutrition	1.63 (0.97-2.74)	3.29 (1.93-5.60)	1.70 (1.08-2.69)	2.12 (1.41-3.20)	4.26 (1.92-9.49)	4.82 (3.09-7.53)

Abbreviations: CDI, *Clostridium difficile* infection; GI, gastrointestinal tract; H_2RA, histamine-2 receptor antagonist; *ICD-9*, *International Classification of Diseases, Ninth Revision*; OR, odds ratios; PPI, proton pump inhibitor.

[a] Data are presented as OR (95% CI) from multivariable regression models using generalized estimating equation with a logit-link (SAS PROC GENMOD). Propensity score and subsequent matching included the following variables: age; sex; admission year; primary diagnosis; *ICD-9*–coded disease states occurring within 48 hours of admission to the intensive care unit; and use of corticosteroids, anticoagulants, platelet inhibitors, or total parenteral nutrition within 48 hours of admission to the intensive care unit. Definitions of disease states and drug therapies are provided in the supplementary information.

chronic kidney injury, trauma, hypertension, acute respiratory failure, and congestive heart failure lost a significant association, whereas shock, sepsis, coronary artery disease, and the use of ampicillin gained a significant relationship (Table 6).

Discussion

This large cohort study demonstrates that the use of PPIs in a heterogeneous population of adult mechanically ventilated patients increases the risks of GI hemorrhage, pneumonia, and CDI compared with the use of H_2RAs. Another key finding of this study indicates that risk factors for GI hemorrhage, pneumonia, and CDI are numerous and occur frequently in this patient population.

The finding that PPIs were more likely to be associated with GI hemorrhage than H_2RAs contradicts our hypothesis that stronger acid suppression reduces GI bleeding. Mechanistically, both drug classes inhibit acid production, but H_2RAs also limit reperfusion injury in animal models, possibly reducing oxidative stress after mucosal injury.[1] The results of recent systematic reviews of trials comparing PPIs and H_2RAs for stress-related mucosal damage suggest the bleeding risk is reduced by approximately 64% with PPIs[8-10]; however, 2 studies with methodological limitations represented nearly 63% of the weight for these comparisons.[28,29] Our results are particularly applicable because they contradict the recommendation by the Surviving Sepsis Campaign favoring PPIs.[30] A large randomized study comparing these 2 classes of agents and powered for clinically significant GI hemorrhage and infectious complications is warranted.

Several of the risk factors we determined for GI hemorrhage are consistent with other studies, including age, acute respiratory failure, shock and/or hypotension, acute kidney injury, chronic hepatic injury, neurologic injury, myocardial infarction, and coagulopathy.[3,31-35] Of interest is the lack of a significant association of several postulated risk factors such as transplant, thermal injury, major surgery or trauma, thrombocytopenia, recent GI hemorrhage, use of corticosteroids, and the use of antiplatelet agents.[1-3] For some of these diseases, the low occurrence rates may have prevented significance (eg, transplant, burns) and/or they lacked definition (eg, trauma). We found hypertension and thrombocytopenia to be protective of hemorrhage, possibly due to enhanced mucosal perfusion and less reperfusion injury.[1-3]

Acid-suppressing agents are traditionally viewed as relatively benign when regimens are short-term; however, recent data indicate they may be associated with pneumonia and CDI, with some studies suggesting that the risk is greatest shortly after starting therapy, as is frequently the case in many critically ill patients.[11-13,16,17] The plausible explanation for this association is that the increased gastric pH generated by acid suppressants may facilitate microbial progression in the GI tract leading to infection.[1-3] Few studies have evaluated the association between acid suppressants and these infectious complications in the inpatient setting. Herzig et al[15] evaluated nearly 64 000 non-ICU hospital admissions and

found that acid suppressants were associated with hospital-acquired pneumonia as defined by *ICD-9* codes. Two systematic reviews found H_2RAs to be associated with pneumonia compared with sucralfate when used in critically ill patients to prevent GI hemorrhage.[36,37] Of note, many of the studies included in these systematic reviews targeted 24-hour pH values of 4 or greater with H_2RA therapy and/or administered H_2RAs by continuous infusion, which may predispose patients to pneumonia. The largest study conducted to date on stress-related mucosal damage included 1200 patients and did not find an increased rate of pneumonia with intermittent dosing of ranitidine compared with sucralfate.[7] For CDI, a recent systematic review of 42 studies and 313 000 patients found that H_2RA therapy was not associated with CDI, but the risk was evident with PPI use and 71% greater compared with H_2RAs.[16] In contrast, the results of a propensity score analysis of more than 100 000 hospital discharges found both PPIs and H_2RAs were associated with CDI toxin-positive infection.[17] To our knowledge, our study is the first to demonstrate that acid suppression, especially with PPIs, is associated with an increased likelihood of pneumonia and CDI when used in mechanically ventilated patients. The risks for these infections were also related to the length of mechanical ventilation. Many of the other risk factors we found for these infections validate what has been described in the literature and likely relate to the overall severity of illness, immunosuppression, previous exposure to and/or colonization with these microbes, or disruption of normal GI flora.

Our overall rates of GI hemorrhage (4.4%), pneumonia (34.2%), and CDI (3.2%) deviate to the high end of other reports. The use of *ICD-9* codes may present questions of validity with respect to disease classification.[38] We extracted the *ICD-9* codes for the outcomes of GI hemorrhage, pneumonia, and CDI from other epidemiologic studies that used similar designs.[15,17,27] In addition, we used multiple codes or combinations of codes for each parameter to enhance sensitivity. We applied numerous exclusion criteria and time restrictions to prevent misclassification (eg, variceal bleed, use of high-dose PPIs at baseline) and improve specificity. We conducted probabilistic sensitivity analyses that demonstrated the robustness of the results to misclassification. Despite these precautions, the observational study design precludes the definitive assignment of outcomes (eg, a GI hemorrhage unrelated to stress-related mucosal damage) or the delineation of the severity of these outcomes (eg, overt vs clinically significant GI hemorrhage).

Several additional limitations are evident when interpreting the results of our study. We speculated that more patients would receive PPI therapy, but we are unable to ascertain why certain regimens were chosen. The univariate analyses showed that baseline demographics and disease state parameters are different between therapies. Our results, however, changed minimally when a propensity matching technique was applied to the models.[25,26] Similarly, we cannot speculate about different institutional practices and the extent they may affect diagnoses and therapies. The most common acid suppressants were famotidine and pantoprazole. While each agent within the drug classes possesses slightly different pharmacodynamics properties, we assumed outcomes were representative of each class of agents. At the time we procured the database, data was only available through December 2008, so any practice or database changes occurring between then and the present have not been captured. For example, an *ICD-9* code for ventilator-associated pneumonia was made available in 2009. The type of data that is available within this database is limited, and while extensive, the database may not apply to all critically ill patients. Clinical data (eg, endoscopy or bronchoscopy) and actual laboratory results are unavailable. We are unable to validate associations between ICU and hospital lengths of stay, mortality, and ICU and hospital costs and GI hemorrhage, pneumonia, or CDI. Lastly, most of the mechanically ventilated patients received an acid suppressant, so we are unable to make comparisons between H_2RAs, PPIs, and no acid suppression.

Conclusions

Proton pump inhibitor therapy is associated with greater risks of GI hemorrhage, pneumonia, and CDI compared with H_2RA therapy in mechanically ventilated patients. Numerous other risk factors have been identified for each of these outcomes. Additional studies are needed to confirm these results.

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