

Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia

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WITH THE ADVENT OF PROTON-pump inhibitors, the use of acid-suppressive medications has increased significantly over the last several years, particularly in the inpatient setting. Studies evaluating the prevalence of acid-suppressive medication estimate that between 40% and 70% of medical inpatients receive some form of acid-suppressive medication during their hospitalization, approximately 50% of which are initiations.^{1,2} Furthermore, approximately half of those newly prescribed acid-suppressive medication in the hospital are subsequently discharged with a prescription for these medications.^{1,3,4}

The high prevalence of acid-suppressive medication use in the inpatient setting is of particular concern for several reasons. First, up to 70% of inpatient use is for indications that have not been investigated or supported by literature, most commonly stress ulcer prophylaxis in low-risk patients.³⁻⁷ Second, recent data in the outpatient setting suggest an increased risk for community-acquired pneumonia in current users of acid-suppressive medication (both proton-pump inhibitors and histamine₂ receptor antagonists).⁸⁻¹⁰ More concerning for the inpatient population are the findings in a cohort of outpatients in the United Kingdom¹⁰; the highest risk for community-acquired pneumonia was within the first 2 days of proton-pump inhibitor therapy, and there was a sta-

Context The use of acid-suppressive medication has been steadily increasing, particularly in the inpatient setting, despite lack of an accepted indication in the majority of these patients.

Objective To examine the association between acid-suppressive medication and hospital-acquired pneumonia.

Design, Setting, and Patients Prospective pharmacoepidemiologic cohort study. All patients who were admitted to a large, urban, academic medical center in Boston, Massachusetts, from January 2004 through December 2007; at least 18 years of age; and hospitalized for 3 or more days were eligible for inclusion. Admissions with time spent in the intensive care unit were excluded. Acid-suppressive medication use was defined as any order for a proton-pump inhibitor or histamine₂ receptor antagonist. Traditional and propensity-matched multivariable logistic regression were used to control for confounders.

Main Outcome Measure Incidence of hospital-acquired pneumonia, defined via codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, in patients exposed and unexposed to acid-suppressive medication.

Results The final cohort comprised 63 878 admissions. Acid-suppressive medication was ordered in 52% of admissions and hospital-acquired pneumonia occurred in 2219 admissions (3.5%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication than in the unexposed group (4.9% vs 2.0%; odds ratio [OR], 2.6; 95% confidence interval [CI], 2.3-2.8). Using multivariable logistic regression, the adjusted OR of hospital-acquired pneumonia in the group exposed to acid-suppressive medication was 1.3 (95% CI, 1.1-1.4). The matched propensity-score analyses yielded identical results. The association was significant for proton-pump inhibitors (OR, 1.3; 95% CI, 1.1-1.4) but not for histamine₂ receptor antagonists (OR, 1.2; 95% CI, 0.98-1.4).

Conclusions In this large, hospital-based pharmacoepidemiologic cohort, acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneumonia. In subset analyses, statistically significant risk was demonstrated only for proton-pump inhibitor use.

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tistically significant association up to 30 days after newly started therapy but no significant association thereafter. Another study⁸ similarly found higher risk among persons who started proton-pump inhibitor use within the prior 7 days. This is particularly concerning given the large proportion of patients who are newly prescribed acid-suppressive medication in the inpatient setting, when they are debilitated and more susceptible to infection.

Despite the recent evidence for adverse outcomes in the outpatient setting and inappropriate prescribing practices in the inpatient setting, these medications con-

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tinue to be frequently prescribed. To our knowledge, no large prospective study has yet examined the association between acid-suppressive medication and hospital-acquired pneumonia in nonventilated patients. We examined this association in a large, prospective pharmacoepidemiologic cohort.

METHODS

Setting and Data Collection

An inception cohort of all patients admitted to a large, urban, academic medical center in Boston, Massachusetts, from January 1, 2004, through December 31, 2007, was investigated. The study was approved by the institutional review board at the medical center and granted a waiver of informed consent. Data were collected from electronic medical information databases maintained at the medical center. These databases, collected prospectively for clinical purposes, contain patient-specific information related to each admission during the study time period. They also include a record of all inpatient medications ordered during each admission.

Inclusion Criteria

All admissions of patients at least 18 years of age and hospitalized for 3 or more days were eligible for inclusion. A cutoff of 3 days was chosen based on the rationale that it would take at least 24 hours of exposure to reliably attribute pneumonia to the acid-suppressive medication exposure, and it would take at least 48 hours of inpatient hospitalization to classify the pneumonia as hospital-acquired, consistent with current criteria of the American Thoracic Society and the Infectious Diseases Society of America.¹¹ To restrict the analysis to the nonventilated, general hospital patient population, admissions with any time spent in the intensive care unit (ICU) were excluded.

Medication Exposure and Outcomes

Acid-suppressive medication exposure was defined as any order for a pharmacy-dispensed proton-pump inhibitor or histamine₂ receptor antagonist during the admission. The day on which

Box. ICD-9-CM Codes Used for Outcomes and Comorbidities	
Outcomes	
Primary outcome	Any pneumonia: 481, 482, 483, 485, 486, 507
Secondary outcomes	Aspiration pneumonia: 507
	Nonaspiration pneumonia: 481, 482, 483, 485, 486
Comorbidities	
The comorbidities in the Charlson Comorbidity Index, ¹² as operationalized by Quan et al, ¹³ were used for the analysis. Following are only the comorbidities that were either added (not already present in the Charlson Comorbidity Index) or enhanced as described in the text.	
Comorbidities not already included in the Charlson Comorbidity Index	
	Gastrointestinal hemorrhage: 578
	Nausea/vomiting: 643, 787.0, 564.3
	Alcohol/drug use: 291, 292, 303, 304, 305
	Psychiatric disorder: 296, 300, 301, 306, 311, 307.8
	Neurologic disorder: 332, 333, 335, 340, 341, 345, 352.1, 352.2, 438.82
Enhanced comorbidities (includes ICD-9-CM codes recommended by Quan et al, ¹³ as well as added ICD-9-CM codes as described in the text)	
	Delirium/dementia: 290, 294.1, 331.2, 293, 294, 331, 797
	Peptic ulcer disease: 530, 531, 532, 533, 534, 535, 536, 787.1, 306.4

these medications were ordered was identified.

The primary outcome was hospital-acquired pneumonia, defined as any discharge code from the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* for bacterial pneumonia listed as a secondary discharge diagnosis (ie, not listed as the primary discharge diagnosis). ICD-9-CM codes used for primary and secondary discharge diagnoses indicating bacterial pneumonia are listed in the BOX. Secondary outcomes included subcategories of hospital-acquired pneumonia: aspiration and nonaspiration pneumonia, also defined via specific ICD-9-CM codes.

Covariates

Covariates were included that were thought to predict use of acid-suppressive medications, as well as variables thought to increase the risk of hospital-acquired pneumonia. These included age; sex; race; season and day of the week of admission;

admitting service (medicine vs other); admission type (elective, urgent, emergent); length of hospitalization; any ICD-9-CM code for gastrointestinal hemorrhage; any ICD-9-CM code for nausea and/or vomiting; and use of specific classes of medications, including drugs with sedating effects (benzodiazepines, barbiturates, antipsychotics, opiates, anesthetics), paralytics, nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled and systemic steroids, and anticoagulant medications (enoxaparin, warfarin, heparin).

Race/ethnicity data were obtained by patient self-report at the time of registration by employees who had received specific training in obtaining and coding this information into fixed categories. These data were included as a variable in the analyses because they may be associated with pneumonia risk.

All of the comorbidities included in the Charlson Comorbidity Index,¹² as operationalized from administrative data by Quan et al,¹³ were controlled for except where noted here. Rather than

use a summary index score, each comorbidity was incorporated into the model as a separate, independent measure, as advocated by Elixhauser et al.¹⁴ Several ICD-9-CM codes were added to the diagnostic categories of dementia and peptic ulcer disease already present in the Charlson comorbidity list to increase the capture rate of these conditions, both hypothesized to have important associations with both acid-suppressive medication exposure and hospital-acquired pneumonia. Additional comorbidities were controlled for, including any ICD-9-CM code for alcohol and/or drug abuse, psychiatric disorders, and neuromuscular disorders, because of the hypothesized association with both acid-suppressive medication use and hospital-acquired pneumonia.

Statistical Analysis

The Fisher exact test was used to compare categorical variables and a non-parametric median test for continuous variables. Unadjusted incidence rates of the primary and secondary outcomes in exposed and unexposed patients were compared using the Fisher exact test.

Patients with multiple admissions would violate the assumption of independence when using logistic regression to analyze the data, so repeated admissions were approached in 2 ways. First, an analysis was performed that included all admissions during the time interval but controlled for confounders and within-participant correlated data using a multivariable generalized estimating equation (GEE) model with logit link and exchangeable working correlation structure. Then a secondary analysis was performed that included only the first admission during the time interval. Because the results obtained with these approaches did not differ, only the results of the first analysis are presented.

In addition, a propensity score was derived¹⁵ using a GEE model with the use of acid-suppressive medication as the dependent variable. In this model, the same set of covariates was used as in the first

approach. The fitted probability from this model was used as the propensity score. This score was assigned to each patient admission reflecting the propensity to have received the exposure of interest. The *c* statistic for the propensity score model was 0.83, indicating a good ability to discriminate between admissions with and without an order for acid-suppressive medication.

Admissions were then matched on their propensity score using a greedy matching technique.¹⁶ With this technique, each admission in which acid-suppressive medication was ordered was matched to the admission with the closest propensity score in which acid-suppressive medication was not ordered, thus addressing confounding by indication. The algorithm specified looking initially for a match out to 6 digits of the propensity score. If a 6-digit match could not be found, the program then moved to 5 digits, then 4, and so on, until the closest match was found. Once admissions were matched on their propensity to have received acid-suppressive medication, baseline characteristics were compared within the matched groups to gauge the effectiveness of the matching. Any baseline characteristics with residual imbalance ($P \leq .05$) were incorporated into a GEE regression model to obtain the adjusted odds ratio (OR) of hospital-acquired pneumonia in the 2 groups.

A 2-sided type I error of 0.05 or less was used to indicate statistical significance for all comparisons. Assuming a rate of 1 hospital-acquired pneumonia per 100 admissions, an estimated sample size of 53 000 admissions would be necessary to achieve 90% power to detect a relative risk of 1.3 in exposed vs unexposed patients. All analyses were carried out using version 9.1 of SAS software (SAS Institute Inc, Cary, North Carolina).

Outcome Sensitivity Analysis and Validation

Because discharge diagnosis codes were used to define the outcome, rather than direct review of the medical record, sensitivity and validation analyses were con-

ducted to ensure that the observed magnitude of any outcome misclassification would not affect interpretation of the results. A sensitivity analysis was conducted to assess the thresholds at which misclassification of the outcome would cause the point estimate of the increased risk of pneumonia to lose clinical significance, which was defined as a 10% increase in the odds of pneumonia. In this simulation, it was sequentially assumed that the misclassification rate of the presence (or absence) of hospital-acquired pneumonia was 1%, 2%, 5%, 7%, and 10%. For example, when the misclassification rate was set at 1%, 1% of the admissions were randomly selected and their outcome was switched from 1 (presence of pneumonia) to 0 (absence of pneumonia) or vice versa. The multivariable model was then rerun using this simulated data to obtain the adjusted OR at each rate of misclassification. This process was repeated to obtain estimates of the OR for all possible combinations of misclassification rates.

In this manner, the misclassification rates (patients coded as having had a pneumonia who on record review did not, and vice versa) that would decrease the effect estimate below the predefined threshold of 1.1 were identified. Once these 2 threshold rates were known, a validation study was performed using medical record review on a randomly selected sample of admissions to estimate the true misclassification rates and their 95% confidence intervals (CIs). If the upper bound of either of these rates exceeded the predetermined thresholds, the implication would be that the estimation result would not be reliable; otherwise the model estimation would be accepted.

Exposure Subgroup and Sensitivity Analyses

In a prespecified subgroup analysis the independent effects of each class of medication on the primary outcome were evaluated. A stratified analysis was performed in which 2 separate multivariable GEE models were run: one examining the effect of proton-pump in-

hibitor exposure excluding patients with exposure to histamine₂ receptor antagonists, and a second examining the effect of histamine₂ receptor antagonist exposure excluding patients with exposure to proton-pump inhibitors. This assessed the independent effects of each of these medication subgroups.

Because there was no information on the date of occurrence of the hospital-acquired pneumonia, it could not be determined whether the acid-suppressive medication was started before or after the onset of pneumonia (if one occurred), raising the possibility of exposure misclassification (ie, if the pneumonia actually occurred before the acid-suppressive medication was started, then the patient should not be considered to have received acid-suppressive medication in accordance with our hypothesis). Therefore, the percentage of orders for acid-suppressive medication that occurred within the first 48 hours of admission was determined; a sensitivity analysis reclassified all admissions in which acid-suppressive medication was not started within the first 48 hours as not having received acid-suppressive medication. The percentage of orders for acid-suppressive medication that occurred within 48 hours of discharge was also ascertained.

Although there was no information on smoking status for the majority of the cohort, there were data in 20 030 admissions (31%). For these admissions, a secondary analysis was performed using a 3-category variable for smoking status (yes, no, and unknown) and running the multivariable GEE model after incorporation of this variable.

RESULTS

Patient Admission Characteristics

There were 136 529 admissions to the medical center from January 1, 2004, through December 31, 2007. After excluding admissions with any time spent in the ICU (n=18 531), as well as admissions with a length of stay less than 3 days (n=54 120), 63 878 admissions comprised the final cohort. Out of 63 878 admissions, there were 42 093 unique patients, indicating repeated ad-

missions ranging from 1 to 61 admissions per patient during the time frame. The median age of the cohort was 54 years (range, 18-107 years), and 23 801 (37%) were men.

Exposure to Acid-Suppressive Medication

Overall, acid-suppressive medication was ordered in 32 922 admissions (52%). Of the group exposed to acid-suppressive

Table 1. Admission Characteristics of Study Population

Variable	Acid-Suppressive Medication (n = 32 922)	No Acid-Suppressive Medication (n = 30 956)
Male, No. (%)	14 759 (45)	9042 (29)
Race or ethnic group, No. (%)		
White	24 709 (75)	21 025 (68)
Black	3473 (11)	3488 (11)
Hispanic	1065 (3)	1242 (4)
Asian	607 (2)	1660 (5)
Other or unknown	3068 (9)	3541 (11)
Age, median (range), y	62 (18-106)	40 (18-107)
Comorbidities, No. (%)		
Myocardial infarction	2399 (7)	1176 (4)
Congestive heart failure	6324 (19)	2611 (8)
Peripheral vascular disease	2546 (8)	1453 (5)
Cerebrovascular disease	1573 (5)	831 (3)
Delirium/dementia	1687 (5)	1097 (4)
Chronic pulmonary disease	6205 (19)	2865 (9)
Connective tissue disease	1165 (4)	384 (1)
Peptic ulcer disease/reflux	7678 (23)	874 (3)
Mild liver disease	2483 (8)	819 (3)
Moderate or severe liver disease	721 (2)	97 (<1)
Diabetes without complications	6562 (20)	3486 (11)
Diabetes with complications	2578 (8)	1364 (4)
Paraplegia/hemiplegia	340 (1)	196 (1)
Renal disease	4622 (14)	1811 (6)
Cancer	5332 (16)	2316 (7)
Metastatic carcinoma	3119 (9)	941 (3)
HIV/AIDS	493 (2)	376 (1)
Alcohol/drug abuse	2712 (8)	1943 (6)
Psychiatric disorder	4499 (14)	3455 (11)
Neuromuscular disorder	1436 (4)	1043 (3)
Gastrointestinal hemorrhage	808 (2)	65 (<1)
Nausea/vomiting	802 (2)	176 (1)
Admitting service, No. (%)		
Medicine	18 702 (57)	8518 (28)
Other	14 220 (43)	22 438 (72)
Admission type, No. (%)		
Elective	6606 (20)	4116 (13)
Emergent	25 163 (76)	14 599 (47)
Urgent	1153 (4)	12 241 (40)
Season of admission, No. (%)		
Winter	7870 (24)	7401 (24)
Spring	8396 (26)	7696 (25)
Summer	8315 (25)	8165 (26)
Fall	8341 (25)	7694 (25)
Length of hospitalization, median (range), d	5 (3-164)	4 (3-170)
In-hospital medications, No. (%)		
Sedative	27 015 (82)	23 842 (77)
NSAID	5924 (18)	14 351 (46)
Steroid, systemic	7314 (22)	1986 (6)
Steroid, inhaled	3840 (12)	1858 (6)
Anticoagulant	22 699 (69)	10 926 (35)

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Rates of Hospital-Acquired Pneumonia According to Acid-Suppressive Medication Status

Outcome	No. (%)		OR (95% CI)		
	Acid-Suppressive Medication (n = 32 922)	No Acid-Suppressive Medication (n = 30 956)	Unadjusted (n = 63 878)	Adjusted (n = 63 878) ^a	Propensity-Matched (n = 32 792) ^b
Hospital-acquired pneumonia	1609 (4.9)	610 (2.0)	2.6 (2.3-2.8)	1.3 (1.1-1.4)	1.3 (1.1-1.4)
Aspiration pneumonia	361 (1.1)	112 (0.4)	3.1 (2.5-3.8)	1.4 (1.1-1.8)	1.4 (1.1-1.8)
Nonaspiration pneumonia	1262 (3.8)	501 (1.6)	2.4 (2.2-2.7)	1.2 (1.1-1.4)	1.2 (1.1-1.4)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAdjusted for all variables listed in Table 1, plus admission day of the week, using a multivariable generalized estimating equation (GEE) to take into account dependency of the data due to repeated admissions.

^bMatched on propensity score and analyzed using a multivariable logistic regression with a GEE, controlling for all significantly imbalanced baseline characteristics after matching, as demonstrated in Table 3 (using $P \leq .05$ to indicate statistical significance).

medications, 27 236 (83%) received proton-pump inhibitors and 7548 (23%) received histamine₂ receptor antagonists, with some exposed to both. The majority of these medications were ordered within 48 hours of admission (29 176; 89%), and an order was still present within 48 hours of discharge in 30 965 (94%). There were significant differences in baseline characteristics between those exposed and unexposed to acid-suppressive medication (TABLE 1).

Relationship of Acid-Suppressive Medication to Hospital-Acquired Pneumonia

TABLE 2 shows the unadjusted incidence rates of hospital-acquired pneumonia relative to acid-suppressive medication status. The primary outcome of hospital-acquired pneumonia occurred in 2219 admissions (3.5%). The unadjusted incidence of hospital-acquired pneumonia was higher in the group exposed to acid-suppressive medication relative to the unexposed group (4.9% vs 2.0%; OR, 2.6; 95% CI, 2.3-2.8). There was a stronger association between acid-suppressive medication and aspiration pneumonia in particular; however, the association remained significant for both aspiration and non-aspiration pneumonia (Table 2).

After adjusting for potential confounders as well as clustering of admissions with a multivariable GEE, the OR of hospital-acquired pneumonia in the group exposed to acid-suppressive medication was 1.3 (95% CI, 1.1-1.4) (Table 2). With respect to the secondary end points of aspiration and non-aspiration pneumonia, the ORs re-

mained significant for each after adjustment, with a stronger association between acid-suppressive medication and aspiration pneumonia than nonaspiration pneumonia (Table 2).

Propensity-Matched Analysis

There was a successful match of 16 396 patient admissions with acid-suppressive medication exposure to 16 396 patient admissions without exposure. After matching admissions by propensity score, the group exposed to acid-suppressive medication was much more similar in baseline characteristics to the unexposed group (TABLE 3). A significant association between exposure to acid-suppressive medication and hospital-acquired pneumonia again existed, with an OR of 1.3 (95% CI, 1.1-1.4) (Table 2). The same association held for the secondary end points of aspiration and nonaspiration pneumonia (Table 2).

Outcome Sensitivity Analysis and Validation

Varying the rate of patients misclassified as having had a pneumonia did not change the point estimate of the OR substantially. This was consistent with only 2219 admissions coded as having had a pneumonia (vs 61 659 without pneumonia); a simulated misclassification rate of 10% among patients originally coded as having had a pneumonia resulted in movement of only 222 admissions to the group without pneumonia and a small change in the OR. Conversely, a simulated misclassification rate of 10% among patients originally coded as not having had a pneumonia resulted in move-

ment of 6166 admissions to the group with pneumonia. In the latter scenario, a misclassification rate of 5% or greater would cause the OR estimate to fall below the predefined threshold of 1.1 and render the results unreliable.

To estimate the actual rate of admissions misclassified as not having had a pneumonia, the discharge summaries of 100 randomly selected admissions that had been classified as not having hospital-acquired pneumonia were reviewed. In the event that there was no discharge summary, the chest radiographs from the admission were reviewed for presence or absence of an infiltrate. Of these 100 admissions, there was 1 case of hospital-acquired pneumonia. This yielded a standard error of 0.01 and a 95% CI upper bound of 2.95%, less than the threshold of 5%.

Exposure Subgroup and Sensitivity Analyses

When examining the association between the subcategories of acid-suppressive medication and hospital-acquired pneumonia in the stratified analysis, the same significant association with hospital-acquired pneumonia held for those exposed to proton-pump inhibitors but not histamine₂ receptor antagonists (TABLE 4). After reclassifying admissions in which acid-suppressive medication was ordered after the first 48 hours of the hospitalization as not having received acid-suppressive medication, the multivariable GEE-derived OR of hospital-acquired pneumonia in an admission with acid-suppressive medication exposure in the first 48 hours was 1.2 (95% CI, 1.04-1.3).

After incorporation of the 3-category variable for smoking into the multivariable GEE model, the adjusted OR and 95% CI for the main effect were unchanged from the baseline analysis (OR, 1.3; 95% CI, 1.1-1.4).

COMMENT

In this large hospital-based pharmacoepidemiologic cohort, use of acid-suppressive medication was associated with 30% increased odds of hospital-acquired pneumonia in nonventilated patients. This association was stronger for aspiration pneumonia than for nonaspiration pneumonia. In a prespecified subgroup analysis, the association was significant for proton-pump inhibitor use but not histamine₂ receptor antagonists.

There are accumulating data implicating an association between acid-suppressive medication and various disease states, including *Clostridium difficile* colitis,¹⁷⁻²⁰ ventilator-associated pneumonia,²¹⁻²⁶ and community-acquired pneumonia.⁸⁻¹⁰ Only 2 of the studies undertaken in critically ill patients have examined the association between proton-pump inhibitors and hospital-acquired pneumonia (the remainder focused exclusively on histamine₂ receptor antagonists, sucralfate, and/or antacids), and neither found a statistically significant association when compared with placebo or histamine₂ receptor antagonists.^{24,27} Both studies, however, were small, and one did not include an unexposed reference group. Given the increased risk of stress-related gastric mucosal ulceration in ventilated patients, acid-suppressive medications continue to be used for prophylactic purposes in this patient population, consistent with current consensus guidelines.²⁸

The theory that non-critically ill hospitalized patients would benefit from stress-ulcer prophylaxis has not been examined in a large, well-designed trial. Accordingly, current guidelines do not support the use of these medications in nonventilated hospitalized patients.²⁸ Studies showing an association between current proton-pump inhibitor use and community-acquired pneumonia found that risk was highest within

the first week of use,^{8,10} of potential importance for the inpatient population in whom initiation of these medica-

tions is frequent. The lack of availability of outpatient medication records in our database precluded assessing

Table 3. Admission Characteristics According to Acid-Suppressive Medication Status After Matching on Propensity Score

Variable	Acid-Suppressive Medication (n = 16 396)	No Acid-Suppressive Medication (n = 16 396)	P Value
Male, No. (%)	7403 (45)	7647 (47)	.007
Race or ethnic group, No. (%)			
White	12 054 (74)	12 052 (74)	.99
Black	1746 (11)	1770 (11)	.68
Hispanic	567 (3)	561 (3)	.88
Asian	371 (2)	340 (2)	.26
Other or unknown	1658 (10)	1673 (10)	.80
Age, median (range), y	59 (18-106)	60 (18-107)	<.001
Comorbidities, No. (%)			
Myocardial infarction	1088 (7)	1104 (7)	.74
Congestive heart failure	2580 (16)	2524 (15)	.40
Peripheral vascular disease	1303 (8)	1361 (8)	.25
Cerebrovascular disease	744 (5)	767 (5)	.56
Delirium/dementia	898 (5)	983 (6)	.05
Chronic pulmonary disease	2436 (15)	2376 (14)	.36
Connective tissue disease	377 (2)	348 (2)	.29
Peptic ulcer disease/reflux	1130 (7)	859 (5)	<.001
Mild liver disease	796 (5)	782 (5)	.74
Moderate or severe liver disease	121 (1)	97 (1)	.12
Diabetes without complications	2949 (18)	3009 (18)	.40
Diabetes with complications	1196 (7)	1232 (8)	.46
Paraplegia/hemiplegia	150 (1)	162 (1)	.53
Renal disease	1790 (11)	1746 (11)	.44
Cancer	2165 (13)	2167 (13)	.99
Metastatic carcinoma	1044 (6)	936 (6)	.01
HIV/AIDS	276 (2)	299 (2)	.35
Alcohol/drug abuse	1402 (9)	1406 (9)	.95
Psychiatric disorder	2233 (14)	2274 (14)	.52
Neuromuscular disorder	748 (5)	771 (5)	.56
Gastrointestinal hemorrhage	87 (1)	65 (<1)	.09
Nausea/vomiting	194 (1)	166 (1)	.15
Admitting service, No. (%)			
Medicine	7812 (48)	7869 (48)	.54
Other	8584 (52)	8527 (52)	.54
Admission type, No. (%)			
Elective	3469 (21)	3599 (22)	.08
Emergent	11 879 (72)	12 169 (74)	<.001
Urgent	1048 (6)	628 (4)	<.001
Season of admission, No. (%)			
Winter	3954 (24)	3949 (24)	.96
Spring	4092 (25)	4093 (25)	>.99
Summer	4274 (26)	4291 (26)	.84
Fall	4076 (25)	4063 (25)	.88
Length of hospitalization, median (range), d	5 (3-71)	4 (3-170)	<.001
In-hospital medications, No. (%)			
Sedative	13 077 (80)	12 939 (79)	.06
NSAID	3364 (21)	2960 (18)	<.001
Steroid, systemic	2039 (12)	1827 (11)	<.001
Steroid, inhaled	1352 (8)	1365 (8)	.81
Anticoagulant	10 281 (63)	10 537 (64)	.003

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Rates of Hospital-Acquired Pneumonia According to Type of Acid-Suppressive Medication

	Acid-Suppressive Medication	No Acid-Suppressive Medication	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Proton-Pump Inhibitors^a				
Total admissions, No.	25 374	30 956	56 330	56 330
Hospital-acquired pneumonia, No. (%)	1340 (5.3)	610 (2.0)	2.8 (2.5-3.1)	1.3 (1.1-1.4) ^b
Histamine₂ Receptor Antagonists^c				
Total admissions, No.	5686	30 956	36 642	36 642
Hospital-acquired pneumonia, No. (%)	176 (3.1)	610 (2.0)	1.6 (1.3-1.9)	1.2 (0.98-1.4) ^b

Abbreviations: CI, confidence interval; OR, odds ratio.

^aPatients prescribed histamine₂ receptor antagonists were excluded from this analysis.

^bAdjusted for all variables listed in Table 1, plus admission day of the week, using a multivariable generalized estimating equation (GEE) to take into account dependency of the data due to repeated admissions.

^cPatients prescribed proton-pump inhibitors were excluded from this analysis.

whether this relationship held in our patient population.

The recent finding of highest risk within the first 2 days of use¹⁰ raises pathophysiologic questions. Acid-suppressive medications have been thought to increase the risk of pneumonia via modification of the upper gastrointestinal flora (and, as a result, respiratory flora) in the setting of a less acidic gastric medium—a process that takes several days to occur.²⁹⁻³² It is possible that even early in this process, pneumonia risk is elevated. The risk might then be expected to remain elevated indefinitely thereafter. However, pneumonia risk appears to decrease with increasing duration of use.⁸⁻¹⁰ These findings should therefore prompt consideration of alternative explanations, such as impairment of white blood cell function associated with proton-pump inhibitor therapy, which has been demonstrated to occur within hours.³³⁻³⁷ Further studies are necessary to elucidate the mechanism of increased pneumonia risk in patients prescribed acid-suppressive medications in general and proton-pump inhibitors in particular.

Acid-suppressive medications, and proton-pump inhibitors in particular, remain frequently prescribed in the inpatient setting outside of the ICU. Our study demonstrated use in 52% of admissions (83% of which were proton-pump inhibitors), similar to the rate estimated in the literature.^{1,2,4-7} With an estimated 40 million discharges from US medical centers each year,³⁸ this suggests approximately 20 million patients

are exposed to these medications annually in the inpatient setting, with potentially important cost implications.³ Estimating that exposure to these medications increases the risk of developing a hospital-acquired pneumonia by 30% (and using OR as relative risk given the rarity of the outcome), with an overall rate of 3.5% and an exposure rate of 52%, this suggests an attributable risk of 0.9%, a number needed to harm of 111, and an excess of more than 180 000 cases of hospital-acquired pneumonia annually that could be attributed to acid-suppressive medication use. With an estimated mortality rate of 18% for hospital-acquired pneumonia,^{39,40} exposure to these medications could result in 33 000 preventable deaths annually. Reduction in the rates of nosocomial infection is one of the top-20 Priority Areas for National Action proposed by the Agency for Healthcare Research and Quality in association with the Institute of Medicine.⁴¹

However, this analysis did not take into account the potential benefits of acid-suppressive medication with respect to prophylaxis of gastrointestinal bleeding. One study examining the incidence of hospital-acquired gastrointestinal bleeding in non-critically ill patients found an incidence of less than 0.5%.⁴² It therefore seems unlikely that the benefit of these medications for gastrointestinal bleed prophylaxis would offset the risk found in our study, but further research is necessary to determine the net clinical effect.

As with all studies using administrative data, there is concern over the va-

lidity of ICD-9-CM coding. Additionally, coding of whether or not a discharge diagnosis was present on admission began toward the end of the study period, and the inability to incorporate this new coding is a limitation of our analysis. To address this, we performed a sensitivity analysis that varied the degree of misclassification of outcomes to investigate the potential effect on the findings. This analysis suggested that our effect estimate was quite robust to even a very high rate of admissions misclassified as having had a pneumonia; although sensitive to a rate of 5% or greater of patients misclassified as not having had a pneumonia, the medical record review suggests that the actual rate of this type of misclassification was below this threshold.

The lack of information on the temporal association between acid-suppressive medication and date of diagnosis of hospital-acquired pneumonia is another study limitation. This was addressed through a sensitivity analysis in which all patients who received their first dose of acid-suppressive medication more than 48 hours into their hospitalization were reclassified as not having received acid-suppressive medication. Although the OR for the main effect decreased from 1.3 to 1.2, some attenuation was expected because this approach biased the result toward the null. Furthermore, for 89% of patients prescribed acid-suppressive medications, they were prescribed within 48 hours of admission, and 94% were still prescribed these medications within 48

hours of discharge, indicating that the duration of use typically spans the hospitalization.

The possibility of unmeasured confounders remains, particularly in light of the large difference between unadjusted and adjusted ORs. There was no available information on activity order, presence of a nasogastric tube, or socioeconomic status, all of which could have an association with both acid-suppressive medication use and hospital-acquired pneumonia. While data on smoking status were not available for the entire cohort, the analysis was repeated after incorporating this information in the subgroup for which it was available; smoking did not confound the observed relationship. Several approaches were used to control for confounders, and 50 covariates were included in the models. The inclusion of length of hospitalization as a covariate introduced a very conservative bias, since hospital-acquired pneumonia itself can prolong length of hospitalization. Despite this, the association between acid-suppressive medication and hospital-acquired pneumonia remained significant after adjusting for length of stay, with no attenuation in effect size. A randomized controlled trial would be helpful to more definitively evaluate the observed relationship, but given the effect estimate, a well-powered trial would require a prohibitively large sample size (approximately 17 000 patients). Although almost 70 000 admissions were studied over a 4-year period, the single-center nature of our study limits generalizability. These findings should thus be validated at other institutions.

While the increased odds of hospital-acquired pneumonia in patients exposed to histamine₂ receptor antagonists was not statistically significant, this subgroup analysis was not adequately powered to detect significance for an OR of less than 1.3. Thus, a small but increased risk associated with this medication subclass cannot be excluded.

CONCLUSIONS

This study found that acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneu-

monia, and this result was significant for proton-pump inhibitor use. These results occur in the context of an increasing body of literature suggesting an association between acid-suppressive medication and pneumonia. Further scrutiny is warranted regarding inpatient prescribing practices of these medications.

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Study concept and design: Herzig, Howell, Ngo, Marcantonio.

Acquisition of data: Herzig, Howell.

Analysis and interpretation of data: Herzig, Howell, Ngo, Marcantonio.

Drafting of the manuscript: Herzig, Ngo.

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Statistical analysis: Herzig, Howell, Ngo.

Obtained funding: Herzig.

Administrative, technical, or material support: Herzig, Howell, Ngo, Marcantonio.

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Let me consider this as a resolution by which I pledge myself to act in all variety of circumstances and to which I must recur often in times of carelessness and temptation—to measure my conduct by the rule of conscience.

—Ralph Waldo Emerson (1803-1882)