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. Furthermore, approximately half of those newly prescribed acid-suppressive medication in the hospital are subsequently discharged with a prescription for these medications.

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. 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). More concerning for the inpatient population are the findings in a cohort of outpatients in the United Kingdom, the highest risk for community-acquired pneumonia was within the first 2 days of proton-pump inhibitor therapy, and there was a statistically significant association up to 30 days after newly started therapy but no significant association thereafter. Another study 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-
continue 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. 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 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; 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, as operationalized from administrative data by Quan et al, were controlled for except where noted here. Rather than

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**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, as operationalized by Quan et al, 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, 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

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use a summary index score, each co-
morbidity was incorporated into the
model as a separate, independent mea-
sure, as advocated by Elixhauser et al.\textsuperscript{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 im-
portant associations with both acid-
suppressive medication exposure and
hospital-acquired pneumonia. Additional comorbidities were controlled for,
including any ICD-9-CM code for al-
cohol and/or drug abuse, psychiatric
disorders, and neuromuscular disor-
ders, because of the hypothesized asso-
ciation with both acid-suppressive
medication use and hospital-acquired
pneumonia.

Statistical Analysis
The Fisher exact test was used to com-
pare categorical variables and a non-
parametric median test for continu-
ous variables. Unadjusted incidence
rates of the primary and secondary out-
comes in exposed and unexposed pa-
tients were compared using the Fisher
exact test.

Patients with multiple admissions
would violate the assumption of inde-
pendence when using logistic regres-
sion to analyze the data, so repeated ad-
missions were approached in 2 ways.
First, an analysis was performed that
included all admissions during the time
interval but controlled for confound-
ers and within-participant correlated
data using a multivariable generalized
estimating equation (GEE) model with
logit link and exchangeable working
correlation structure. Then a second-
ary analysis was performed that in-
cluded only the first admission during
the time interval. Because the results ob-
tained with these approaches did not
differ, only the results of the first analy-
sis are presented.

In addition, a propensity score was de-
derived\textsuperscript{15} using a GEE model with the use of
acid-suppressive medication as the de-
pendent 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 abil-
ity 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.\textsuperscript{16} With this tech-
nique, 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 or-
dered, thus addressing confounding by
indication. The algorithm specified
looking initially for a match out to 6 dig-
its of the propensity score. If a 6-digit
match could not be found, the pro-
gram 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 effec-
tiveness of the matching. Any baseline
characteristics with residual imbal-
ance \(( P \leq .05)\) 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 signifi-
cance for all comparisons. Assuming a
rate of 1 hospital-acquired pneumo-
nia 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, sen-
sitivity and validation analyses were con-
ducted to ensure that the observed mag-
nitude of any outcome misclassification
would not affect interpretation of the re-
sults. A sensitivity analysis was con-
ducted to assess the thresholds at which
misclassification of the outcome would
cause the point estimate of the in-
creased risk of pneumonia to lose clin-
ical significance, which was defined as a
10% increase in the odds of pneu-
nonia. In this simulation, it was sequen-
tially assumed that the misclassifica-
tion 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 ran-
domly selected and their outcome was
switched from 1 (presence of pneu-
nonia) to 0 (absence of pneumonia) or vice versa. The multivariable model was then
rerun using this simulated data to ob-
tain the adjusted OR at each rate of mis-
classification. This process was re-
peated to obtain estimates of the OR for
all possible combinations of misclassifi-
cation rates.

In this manner, the misclassifica-
tion rates (patients coded as having had
a pneumonia who on record review did
not, and vice versa) that would de-
crease the effect estimate below the pre-
defined threshold of 1.1 were identi-
fied. Once these threshold rates were
known, a validation study was per-
formed using medical record review on
a randomly selected sample of admis-
sions to estimate the true misclassifi-
cation rates and their 95% confidence
intervals (CIs). If the upper bound of
either of these rates exceeded the pre-
determined thresholds, the implica-
tion would be that the estimation re-
sult 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 multi-
variable GEE models were run: one ex-
amining the effect of proton-pump in-

\( \text{ICD-9-CM} \) 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 im-
portant associations with both acid-
suppressive medication exposure and
hospital-acquired pneumonia. Additional comorbidities were controlled for,
including any ICD-9-CM code for al-
cohol and/or drug abuse, psychiatric
disorders, and neuromuscular disor-
ders, because of the hypothesized asso-
ciation with both acid-suppressive
medication use and hospital-acquired
pneumonia.
inhibitor exposure excluding patients with exposure to histamine$_2$ receptor antagonists, and a second examining the effect of histamine$_2$ 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. Of 63,878 admissions, there were 42,093 unique patients, indicating repeated admissions 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acid-Suppressive Medication (n = 32,922)</th>
<th>No Acid-Suppressive Medication (n = 30,956)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>14,759 (45)</td>
<td>9,042 (29)</td>
</tr>
<tr>
<td>Race or ethnic group, No. (%)</td>
<td>White 24,709 (75)</td>
<td>21,025 (68)</td>
</tr>
<tr>
<td></td>
<td>Black 3,473 (11)</td>
<td>3,488 (11)</td>
</tr>
<tr>
<td></td>
<td>Hispanic 1,065 (3)</td>
<td>1,242 (4)</td>
</tr>
<tr>
<td></td>
<td>Asian 607 (2)</td>
<td>1,660 (5)</td>
</tr>
<tr>
<td></td>
<td>Other or unknown 3,068 (9)</td>
<td>3,541 (11)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>62 (18-106)</td>
<td>40 (18-107)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td>Myocardial infarction 2,399 (7)</td>
<td>1,176 (4)</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure 6,324 (19)</td>
<td>2,611 (8)</td>
</tr>
<tr>
<td></td>
<td>Peripheral vascular disease 2,546 (8)</td>
<td>1,453 (5)</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease 1,573 (5)</td>
<td>831 (3)</td>
</tr>
<tr>
<td></td>
<td>Delirium/dementia 1,687 (5)</td>
<td>1,097 (4)</td>
</tr>
<tr>
<td></td>
<td>Chronic pulmonary disease 6,205 (19)</td>
<td>2,865 (9)</td>
</tr>
<tr>
<td></td>
<td>Connective tissue disease 1,165 (4)</td>
<td>384 (1)</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer disease/reflux 7,678 (23)</td>
<td>874 (3)</td>
</tr>
<tr>
<td></td>
<td>Mild liver disease 2,483 (8)</td>
<td>819 (3)</td>
</tr>
<tr>
<td></td>
<td>Moderate or severe liver disease 721 (2)</td>
<td>97 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Diabetes without complications 6,662 (20)</td>
<td>3,486 (11)</td>
</tr>
<tr>
<td></td>
<td>Diabetes with complications 2,578 (8)</td>
<td>1,364 (4)</td>
</tr>
<tr>
<td></td>
<td>Paraplegia/hemiplegia 340 (1)</td>
<td>196 (1)</td>
</tr>
<tr>
<td></td>
<td>Renal disease 4,622 (14)</td>
<td>1,811 (6)</td>
</tr>
<tr>
<td></td>
<td>Cancer 5,332 (16)</td>
<td>2,316 (7)</td>
</tr>
<tr>
<td></td>
<td>Metastatic carcinoma 3,119 (9)</td>
<td>941 (3)</td>
</tr>
<tr>
<td></td>
<td>HIV/AIDS 493 (2)</td>
<td>376 (1)</td>
</tr>
<tr>
<td></td>
<td>Alcohol/drug abuse 2,712 (8)</td>
<td>1,943 (6)</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorder 4,499 (14)</td>
<td>3,455 (11)</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular disorder 1,436 (4)</td>
<td>1,043 (3)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal hemorrhage 808 (2)</td>
<td>66 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting 802 (2)</td>
<td>176 (1)</td>
</tr>
<tr>
<td>Admitting service, No. (%)</td>
<td>Medicine 18,702 (57)</td>
<td>8,518 (29)</td>
</tr>
<tr>
<td></td>
<td>Other 14,220 (43)</td>
<td>22,438 (72)</td>
</tr>
<tr>
<td>Admission type, No. (%)</td>
<td>Elective 6,606 (20)</td>
<td>4,116 (13)</td>
</tr>
<tr>
<td></td>
<td>Emergent 25,163 (76)</td>
<td>14,599 (47)</td>
</tr>
<tr>
<td></td>
<td>Urgent 1,153 (4)</td>
<td>12,241 (40)</td>
</tr>
<tr>
<td>Season of admission, No. (%)</td>
<td>Winter 7,870 (24)</td>
<td>7,401 (24)</td>
</tr>
<tr>
<td></td>
<td>Spring 8,396 (26)</td>
<td>7,696 (25)</td>
</tr>
<tr>
<td></td>
<td>Summer 8,315 (25)</td>
<td>8,165 (26)</td>
</tr>
<tr>
<td></td>
<td>Fall 8,341 (25)</td>
<td>7,694 (25)</td>
</tr>
<tr>
<td>Length of hospitalization, median (range), d</td>
<td>5 (3-164)</td>
<td>4 (3-170)</td>
</tr>
<tr>
<td>In-hospital medications, No. (%)</td>
<td>Sedative 27,015 (82)</td>
<td>23,842 (77)</td>
</tr>
<tr>
<td></td>
<td>NSAID 5,924 (18)</td>
<td>14,391 (46)</td>
</tr>
<tr>
<td></td>
<td>Steroid, systemic 7,314 (22)</td>
<td>1,986 (6)</td>
</tr>
<tr>
<td></td>
<td>Steroid, inhaled 3,840 (12)</td>
<td>1,858 (6)</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant 22,690 (69)</td>
<td>10,926 (35)</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.
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 nonaspiration 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 nonaspiration pneumonia, the ORs remained 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 a simulated OR of 1.3 (95% CI, 1.1-1.4) (Table 2). With respect to the secondary end points of aspiration and nonaspiration pneumonia, the ORs remained significant for each after adjustment, with a stronger association between acid-suppressive medication and aspiration pneumonia than nonaspiration pneumonia (Table 2).

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).

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Acid-Suppressive Medication (n = 32,922)</th>
<th>No Acid-Suppressive Medication (n = 30,956)</th>
<th>Unadjusted (n = 63,878)</th>
<th>Adjusted (n = 63,878)</th>
<th>Propensity-Matched (n = 32,792)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital-acquired pneumonia</td>
<td>1609 (4.9)</td>
<td>610 (2.0)</td>
<td>2.6 (2.3-2.8)</td>
<td>1.3 (1.1-1.4)</td>
<td>1.3 (1.1-1.4)</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>361 (1.1)</td>
<td>112 (0.4)</td>
<td>3.1 (2.5-3.8)</td>
<td>1.4 (1.1-1.8)</td>
<td>1.4 (1.1-1.8)</td>
</tr>
<tr>
<td>Nonaspiration pneumonia</td>
<td>1262 (3.8)</td>
<td>501 (1.6)</td>
<td>2.4 (2.2-2.7)</td>
<td>1.2 (1.1-1.4)</td>
<td>1.2 (1.1-1.4)</td>
</tr>
</tbody>
</table>

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

a Adjusted 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.

b Matched 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 ≤ .05 to indicate statistical significance).
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 histamine receptor antagonists.

There are accumulating data implicating an association between acid-suppressive medication and various disease states, including *Clostridium difficile* colitis, ventilator-associated pneumonia, and community-acquired pneumonia. 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 histamine, receptor antagonists, succralate, and/or antacids), and neither found a statistically significant association when compared with placebo or histamine, receptor antagonists. 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.

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. 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, of potential importance for the inpatient population in whom initiation of these medications 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acid-Suppressive Medication (n = 16,396)</th>
<th>No Acid-Suppressive Medication (n = 16,396)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>7453 (45)</td>
<td>7647 (47)</td>
<td>.007</td>
</tr>
<tr>
<td>Race or ethnic group, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12,054 (74)</td>
<td>12,052 (74)</td>
<td>.99</td>
</tr>
<tr>
<td>Black</td>
<td>1746 (11)</td>
<td>1770 (11)</td>
<td>.68</td>
</tr>
<tr>
<td>Hispanic</td>
<td>567 (3)</td>
<td>561 (3)</td>
<td>.88</td>
</tr>
<tr>
<td>Asian</td>
<td>371 (2)</td>
<td>340 (2)</td>
<td>.26</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>1658 (10)</td>
<td>1673 (10)</td>
<td>.80</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>59 (18-106)</td>
<td>60 (18-107)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1088 (7)</td>
<td>1104 (7)</td>
<td>.74</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2580 (16)</td>
<td>2524 (15)</td>
<td>.40</td>
</tr>
<tr>
<td>Peripher al vascular disease</td>
<td>1303 (8)</td>
<td>1361 (8)</td>
<td>.25</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>744 (5)</td>
<td>767 (5)</td>
<td>.56</td>
</tr>
<tr>
<td>Delirium/dementia</td>
<td>898 (5)</td>
<td>983 (6)</td>
<td>.05</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>2436 (15)</td>
<td>2376 (14)</td>
<td>.36</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>377 (2)</td>
<td>348 (2)</td>
<td>.29</td>
</tr>
<tr>
<td>Peptic ulcer disease/reflux</td>
<td>1130 (7)</td>
<td>859 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>796 (5)</td>
<td>782 (5)</td>
<td>.74</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>121 (1)</td>
<td>97 (1)</td>
<td>.12</td>
</tr>
<tr>
<td>Diabetes without complications</td>
<td>2049 (13)</td>
<td>3009 (18)</td>
<td>.40</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>1196 (7)</td>
<td>1323 (8)</td>
<td>.46</td>
</tr>
<tr>
<td>Paraplegia/parempilegia</td>
<td>150 (1)</td>
<td>162 (1)</td>
<td>.53</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1790 (11)</td>
<td>1746 (11)</td>
<td>.44</td>
</tr>
<tr>
<td>Cancer</td>
<td>2165 (13)</td>
<td>2167 (13)</td>
<td>.99</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>1044 (6)</td>
<td>936 (6)</td>
<td>.01</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>276 (2)</td>
<td>299 (2)</td>
<td>.35</td>
</tr>
<tr>
<td>Alcohol/drug abuse</td>
<td>1402 (9)</td>
<td>1406 (9)</td>
<td>.95</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2233 (14)</td>
<td>2274 (14)</td>
<td>.52</td>
</tr>
<tr>
<td>Neuromuscular disorder</td>
<td>748 (5)</td>
<td>771 (5)</td>
<td>.56</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>87 (1)</td>
<td>65 (&lt;1)</td>
<td>.09</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>194 (1)</td>
<td>166 (1)</td>
<td>.15</td>
</tr>
<tr>
<td>Admitting service, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>7812 (48)</td>
<td>7869 (48)</td>
<td>.54</td>
</tr>
<tr>
<td>Other</td>
<td>8584 (52)</td>
<td>8527 (52)</td>
<td>.54</td>
</tr>
<tr>
<td>Admission type, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>3469 (21)</td>
<td>3599 (22)</td>
<td>.08</td>
</tr>
<tr>
<td>Emergent</td>
<td>11,879 (72)</td>
<td>12,169 (74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Urgent</td>
<td>1048 (6)</td>
<td>628 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Season of admission, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>3954 (24)</td>
<td>3949 (24)</td>
<td>.96</td>
</tr>
<tr>
<td>Spring</td>
<td>4092 (25)</td>
<td>4093 (25)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Summer</td>
<td>4274 (26)</td>
<td>4291 (26)</td>
<td>.84</td>
</tr>
<tr>
<td>Fall</td>
<td>4076 (25)</td>
<td>4063 (25)</td>
<td>.88</td>
</tr>
<tr>
<td>Length of hospitalization, median (range), d</td>
<td>5 (3-71)</td>
<td>4 (3-170)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>In-hospital medications, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative</td>
<td>13,077 (80)</td>
<td>12,939 (79)</td>
<td>.06</td>
</tr>
<tr>
<td>NSAID</td>
<td>3364 (21)</td>
<td>2960 (18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steroid, systemic</td>
<td>2039 (12)</td>
<td>1827 (11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steroid, inhaled</td>
<td>1352 (8)</td>
<td>1365 (8)</td>
<td>.81</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>10,281 (63)</td>
<td>10,537 (64)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drug.
whether this relationship held in our patient population. The recent finding of highest risk within the first 2 days of use\textsuperscript{10} 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.\textsuperscript{20-23} 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.\textsuperscript{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.\textsuperscript{33,34} 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.\textsuperscript{1,2,4-7} With an estimated 40 million discharges from US medical centers each year,\textsuperscript{38} this suggests approximately 20 million patients are exposed to these medications annually in the inpatient setting, with potentially important cost implications.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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\%.\textsuperscript{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 validity 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

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

<table>
<thead>
<tr>
<th>Acid-Suppressive Medication</th>
<th>No Acid-Suppressive Medication</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton-Pump Inhibitors\textsuperscript{a}</td>
<td>Total admissions, No.</td>
<td>25 374</td>
<td>30 956</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia, No. (%)</td>
<td>1340 (5.3)</td>
<td>610 (2.0)</td>
<td>2.8 (2.5-3.1)</td>
</tr>
<tr>
<td>Total admissions, No.</td>
<td>Histamine, Receptor Antagonists\textsuperscript{c}</td>
<td>5686</td>
<td>30 956</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia, No. (%)</td>
<td>176 (3.1)</td>
<td>610 (2.0)</td>
<td>1.6 (1.3-1.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.\textsuperscript{a} Patients prescribed histamine, receptor antagonists were excluded from this analysis.\textsuperscript{b} Adjusted 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.\textsuperscript{c} Patients prescribed proton-pump inhibitors were excluded from this analysis.
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 naso-gastric 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 histamine<sub>2</sub> 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 pneumonia, 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.

Author Contributions: Dr Herzig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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

Acquisition of data: Herzig, Howell, Ngo, Marcantonio.

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

Drafting of the manuscript: Herzig, Ngo, Marcantonio.

Critical revision of the manuscript for important intellectual content: Herzig, Howell, Ngo, Marcantonio.

Statistical analysis: Herzig, Howell, Ngo.

Obtained funding: Herzig.

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

Study supervision: Herzig, Marcantonio.

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Disclaimer: The study contents are solely the responsibility of the authors and do not necessarily represent the official views of the Department of Health and Human Services.

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ACID-SUPPRESSIVE MEDICATION AND HOSPITAL-ACQUIRED PNEUMONIA


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)