Risk Factors for Nosocomial Gastrointestinal Bleeding and Use of Acid-Suppressive Medication in Non-Critically Ill Patients

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BACKGROUND: It is unknown whether there exist certain subsets of patients outside of the intensive care unit in whom the risk of nosocomial gastrointestinal bleeding is high enough that prophylactic use of acid-suppressive medication may be warranted.

OBJECTIVE: To identify risk factors for nosocomial gastrointestinal bleeding in a cohort of non-critically ill hospitalized patients, develop a risk scoring system, and use this system to identify patients most likely to benefit from acid suppression.

DESIGN: Cohort study.

PATIENTS: Adult patients admitted to an academic medical center from 2004 through 2007. Admissions with a principal diagnosis of gastrointestinal bleeding or a principal procedure code for cardiac catheterization were excluded.

MAIN MEASURES: Medication, laboratory, and other clinical data were obtained through electronic data repositories maintained at the medical center. The main outcome measure—nosocomial gastrointestinal bleeding occurring outside of the intensive care unit—was ascertained via ICD-9-CM coding and confirmed by chart review.

KEY RESULTS: Of 75,723 admissions (median age = 56 years; 40 % men), nosocomial gastrointestinal bleeding occurred in 203 (0.27 %). Independent risk factors for bleeding included age > 60 years, male sex, liver disease, acute renal failure, sepsis, being on a medicine service, prophylactic anticoagulants, and coagulopathy. Risk of bleeding increased as clinical risk score derived from these factors increased. Acid-suppressive medication was utilized in > 50 % of patients in each risk stratum. Our risk scoring system identified a high risk group in whom the number-needed-to-treat with acid-suppressive medication to prevent one bleeding event was < 100.

CONCLUSIONS: In this large cohort of non-critically ill hospitalized patients, we identified several independent risk factors for nosocomial gastrointestinal bleeding. With further validation at other medical centers, the risk model derived from these factors may help clinicians to direct acid-suppressive medication to those most likely to benefit..

KEY WORDS: gastrointestinal bleeding; acid suppression; antiulcer agents.
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INTRODUCTION

Acid-suppressive medication has been demonstrated to reduce the incidence of clinically significant nosocomial gastrointestinal bleeding in hospitalized patients, both in and outside of the intensive care unit (ICU).[1,2] However, owing to sparse data on the incidence of this complication in patients outside of the ICU, current guidelines recommend against routine use of acid-suppressive medication to prevent stress ulceration in non-critically ill hospitalized patients.[3] Recently, studies on the epidemiology of nosocomial gastrointestinal bleeding in non-critically ill patients have added support to this recommendation, finding a low overall incidence of 0.3–0.4 % in this setting.[2,4] While these data support the current recommendations against routine use of acid-suppressive medication for prophylactic purposes in average risk patients outside of the ICU, there may be certain subsets of patients in whom the risk of nosocomial gastrointestinal bleeding is high enough that prophylactic use of acid-suppressive medication may be warranted.

Prior studies in the ICU setting investigating risk factors for nosocomial gastrointestinal bleeding have consistently identified mechanical ventilation and coagulopathy as significant independent predictors, both of which confer high enough risk to warrant prophylactic acid-suppressive medication in this patient population.[5–7] Whether similar

risk factors exist in non-critically ill patients has not been well examined. Such information is crucial to aid clinicians in more appropriate use of acid-suppressive medication.

We sought to identify independent predictors of nosocomial gastrointestinal bleeding in a large cohort of non-critically ill hospitalized patients, and to use this information to develop a clinical risk scoring system. We then derived numbers-needed-to-treat with acid-suppressive medication to prevent one episode of nosocomial gastrointestinal bleeding at increasing levels of clinical risk, in an effort to inform clinical decision making around acid-suppressive medication use in the non-critically ill hospitalized patient.

METHODS

Setting and Data Collection

We studied admissions to a large academic medical center in Boston, Massachusetts from January 2004 through December 2007. The study was approved by the institutional review board and granted a waiver of informed consent. Data were obtained from the medical center's electronic medical information databases, which are collected prospectively for clinical purposes and contain patient-specific information for each admission.

Inclusion and Exclusion Criteria

We included all admissions of patients ≥ age 18 who were hospitalized for ≥ 3 days. We chose 3 days to allow sufficient time for development of nosocomial gastrointestinal bleeding. We excluded admissions with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for gastrointestinal hemorrhage listed as the principal discharge diagnosis. We reviewed the charts of all admissions where gastrointestinal hemorrhage was listed as a secondary discharge diagnosis, and excluded cases where gastrointestinal bleeding occurred within 24 h of admission. We also excluded admissions with a principal procedure code for cardiac catheterization, since these patients are transiently exposed to high doses of unconventional antiplatelet and anticoagulant medications that were unable to be accounted for in our analysis, and represent a unique patient population, already investigated in other published studies.[8–10] Other common percutaneous vascular and surgical procedures involve standard anticoagulants with traditional monitoring, allowing capture in our data set.

Nosocomial Gastrointestinal Bleeding Outcome

The primary outcome was nosocomial gastrointestinal bleeding occurring outside of the ICU, defined as any overt gastrointestinal bleeding (hematemesis, nasogastric aspirate containing "coffee grounds" material, melena, or hematochezia) occurring greater than 24 h after admission, in a patient outside of the ICU. Potential cases were ascertained via ICD-9-CM coding with subsequent chart review to ensure 100 % specificity of our outcome. We excluded from our outcome definition bleeding episodes occurring during an ICU stay or within 48 h of transfer out of the ICU, as well as bleeding documented by the treating physicians as having originated from anatomic locations other than the upper gastrointestinal tract. Previously, we confirmed that this outcome measure had high sensitivity and low levels of misclassification.[2]

Risk Factors

Clinical variables with a hypothesized association with gastrointestinal bleeding were included as candidate risk factors. These included: 1) demographic variables; 2) comorbid conditions, derived from the individual variables included in the Charlson Comorbidity Index,[11] as operationalized from administrative data by Quan et al.,[12] in addition to several conditions categorized by the Agency for Healthcare Research and Quality's Clinical Classifications Software,[13] including septicemia, pneumonia, and acute and unspecified renal failure (modified to exclude unspecified renal failure—ICD-9-CM code 586.xx—as it was already included in our chronic and unspecified renal disease variable); 3) service of care; 4) laboratory markers of coagulopathy, including platelet count, international normalized ratio (INR), and partial thromboplastin time (PTT); and 5) receipt of specific medications during hospitalization, including acid-suppressive medications (histamine-2 receptor antagonist or proton-pump inhibitor), nonsteroidal anti-inflammatory drugs (NSAIDs), systemic steroids (high dose defined as > 200 mg or the equivalent of hydrocortisone per day; low dose defined as ≤ 200 mg or the equivalent per day),[6] antiplatelet medications (aspirin, clopidogrel), prophylactic anticoagulants (subcutaneous heparin and ≤ 60 mg per day of enoxaparin) and therapeutic anticoagulants not already represented by the laboratory markers of coagulopathy (fondaparinux and > 60 mg per day of enoxaparin). Intravenous heparin, warfarin, lepirudin, and argatroban were not included as separate variables, because the effects of these medications on bleeding were already accounted for via laboratory markers of coagulopathy.

Medical records were reviewed to assure that ICD-9-CM-derived comorbidities and medication exposures preceded the episode of bleeding. Comorbidities, medications, and laboratory values were censored at the occurrence of gastrointestinal bleeding. For laboratory values, we used the most extreme value prior to a bleeding episode, or during the entire hospitalization for those without bleeding (lowest platelet value, highest INR, highest PTT), to represent the hypothesized period of greatest susceptibility. When laboratory values were unavailable, we assumed a value within the center of the normal reference range for our laboratory.

Statistical Analysis

Unadjusted associations between candidate risk factors and gastrointestinal bleeding were assessed using Fisher's Exact test. We used multivariate logistic regression to model the association between candidate risk factors and nosocomial gastrointestinal bleeding.

We included two multicategory variables in our models. First, because we were interested in the effect of high versus low dose systemic steroids, we used a three category variable in our models, where no exposure to steroids was the reference group. Second, we were interested in examining combinations of coagulopathy and aspirin and clopidogrel therapy because the latter two are often used together, and could have a synergistic effect on bleeding risk, especially in the presence of coagulopathy. We defined coagulopathy as presence of any one of the following: platelet count < 50,000 cells/μL, INR > 1.5, PTT > 2 times control, or use of a therapeutic anticoagulant which does not affect laboratory markers of coagulopathy (enoxaparin at doses of > 60 mg per day or fondaparinux). We then developed a six category variable representing mutually-exclusive combinations: single antiplatelet therapy (aspirin or clopidogrel); dual antiplatelet therapy (aspirin and clopidogrel); coagulopathy in the absence of antiplatelet therapy with aspirin or clopidogrel; coagulopathy with single antiplatelet therapy; coagulopathy with dual antiplatelet therapy. The final category, defined as absence of the previous categories, served as the reference group.

We randomly assigned 80 % of the admissions in our cohort to a "derivation cohort," and 20 % to a "validation cohort." We used the derivation cohort to develop a multivariable logistic regression model for nosocomial gastrointestinal bleeding including all candidate predictor variables, from which we retained in the final model only those variables with a p value < 0.05. Age was dichotomized at 60 to facilitate development of our risk score. We used the area under the receiver operating characteristic curve (c-statistic) to assess performance of our final model in the derivation and validation cohorts.

The odds ratios of variables with a significant, independent relationship with nosocomial gastrointestinal bleeding in our final model were used to construct a risk score. Each odds ratio from the final model was converted into points by rounding to the nearest integer. The risk score for an individual patient was determined by adding the points for each factor present. Although acid-suppressive medication was included in the final multivariable model from which our odds ratios and corresponding points were derived, we excluded this variable from our risk score calculation. Thus, while the odds ratios and associated points reflect the independent effect of each variable adjusted for all other variables in the final model, the final risk score for any given patient represents the risk of bleeding in the absence of acid-suppressive medication. This allowed for stratification of risk of bleeding by acid-suppressive medication treatment status within different risk categories.

To derive clinically meaningful representations of risk, and the effect of acid-suppressive medication, we determined the risk of bleeding stratified by acid-suppressive medication status in each of four risk categories, and at increasing risk score thresholds. We used these stratified estimates of bleeding risk to calculate the absolute risk difference and corresponding number-needed-to-treat with acid-suppressive medication to prevent one episode of nosocomial gastrointestinal bleeding in each risk category.

All analyses were carried out using SAS software, version 9.1.3, Cary, NC.

Sensitivity Analyses

Because not all overt bleeding episodes are clinically significant, we evaluated the ability of our final model to predict clinically significant bleeding, which we previously operationalized as overt bleeding with the additional requirement of either an *ICD-9-CM* procedure code for upper endoscopy or receipt of at least two units of packed red blood cells during the admission.[2]

Additionally, because a large proportion of our sample was exposed to acid-suppressive medication, and we aimed to develop a model to aid clinicians in deciding upon de novo therapy, we assessed performance of our model in patients unexposed to acid-suppressive medication.

RESULTS

Patient Admission Characteristics

There were 136,529 adult admissions to the medical center from January 1, 2004 through December 31, 2007. After excluding admissions with a length of stay < 3 days (n= 56,430), admissions where gastrointestinal hemorrhage was present on admission (n=1,705), and admissions with a principal procedure code of cardiac catheterization (n= 2,671), 75,723 admissions were available for analysis. Eighty percent were randomly assigned to the derivation (n=60,578) and 20 % to the validation set (n=15,145). Patient characteristics were similar in both sets (see online appendix Table). Table 1 displays characteristics of the derivation set. The median age was 56 years (range 18–107 years), and 24,072 (40 %) were men. Acid-suppressive medication was administered in 35,282 (58 %) admissions, of which 28,610 (81 %) received a proton-pump inhibitor and 10,344 (29 %) received a histamine-2 receptor antagonist, with some receiving both. Nosocomial gastrointestinal bleeding occurred in 203 (0.27 %) admissions in the overall cohort, and 159 (0.26 %) admissions in the derivation set.

Table 1. Admission Characteristics and Unadjusted Associations with Bleeding in the Derivation Cohort

Risk factor	Overall (n=60,578)	Bleeding (n=159)	No bleeding (n=60,419)	p value*
Age > 60 years	25,778 (43)	119 (75)	25,659 (42)	< 0.001
Male	24,072 (40)	95 (60)	23,977 (40)	< 0.001
Race				
White	43,539 (72)	115 (72)	43,424 (72)	
Black	6,417 (11)	19 (12)	6,398 (11)	0.75
Other or unknown	10,622 (18)	25 (16)	10,597 (18)	
Comorbidities				
Myocardial infarction	3,448 (6)	12 (8)	3,436 (6)	0.3
Congestive heart failure	9,806 (16)	63 (40)	9,743 (16)	< 0.001
Peripheral vascular disease	4,357 (7)	21 (13)	4,336 (7)	0.008
Cerebrovascular disease	3,105 (5)	14 (9)	3,091 (5)	0.05
Dementia	986 (2)	3 (2)	983 (2)	0.75
Chronic pulmonary disease	9,281 (15)	27 (17)	9,254 (15)	0.58
Connective tissue disease	1,490 (2)	6 (4)	1,484 (2)	0.28
Diabetes without complications	9,972 (16)	42 (26)	9,930 (16)	0.002
Diabetes with complications	3,719 (6)	18 (11)	3,701 (6)	0.01
Paraplegia/hemiplegia	613 (1)	0 (0)	613 (1)	0.42
Liver disease	3,561 (6)	25 (16)	3,536 (6)	< 0.001
Acute renal failure	6,414 (11)	59 (37)	6,355 (11)	< 0.001
Chronic and unspecified renal failure	6,360 (11)	39 (25)	6,321 (10)	< 0.001
Cancer	7,374 (12)	27 (17)	7,347 (12)	0.07
Metastatic carcinoma	3,860 (6)	13 (8)	3,847 (6)	0.33
HIV/AIDS	820 (1)	3 (2)	817 (1)	0.48
Prior peptic ulcer	52 (0)	0 (0)	52 (0)	1
Pneumonia	4,269 (7)	20 (13)	4,249 (7)	0.01
Sepsis	3,318 (5)	30 (19)	3,288 (5)	< 0.001
Service				
Non-medicine	36,040 (59)	34 (21)	36,006 (60)	< 0.001
Medicine†	24,538 (41)	125 (79)	24,413 (40)	
In-hospital medications and coagulopathy				
Acid-suppressive medication	35,282 (58)	111 (70)	35,171 (58)	0.003
NSAID/COX2 inhibitor	18,881 (31)	17 (11)	18,864 (31)	< 0.001
Steroids				
None	50,694 (84)	117 (74)	50,577 (84)	
Low dose‡	4,093 (7)	17 (11)	4,076 (7)	0.003
High dose§	5,791 (10)	25 (16)	5,766 (10)	
Prophylactic anticoagulant‖	30,066 (50)	108 (68)	29,958 (50)	< 0.001
Antiplatelet/coagulopathy combinations,				
No antiplatelet agent, no coagulopathy	35,714 (59)	36 (23)	35,678 (59)	
Single antiplatelet agent¶ without coagulopathy	8,941 (15)	27 (17)	8,914 (15)	
Dual antiplatelet agents# without coagulopathy	1,991 (3)	8 (5)	1,983 (3)	< 0.001
Coagulopathy** without antiplatelet agents	7,291 (12)	40 (25)	7,251 (12)	
Coagulopathy with single antiplatelet agent	4,973 (8)	37 (23)	4,936 (8)	
Coagulopathy with dual antiplatelet agents	1,668 (3)	11 (7)	1,657 (3)	

COX2 cyclooxygenase 2; HIV/AIDS human immunodeficiency virus/acquired immunodeficiency syndrome; NSAID non-steroidal anti-inflammatory drugs
Data are given as number (%) of patients unless otherwise specified
**p-value reflects comparison of patients with and without bleeding*
†All services other than general surgery, surgical subspecialties, obstetrics and gynecology, neurology, psychiatry
‡≤200 mg/day of hydrocortisone or the equivalent
§>200 mg/day of hydrocortisone or the equivalent
‖ Subcutaneous unfractionated heparin and ≤60 mg/day of enoxaparin
¶Aspirin or clopidogrel
#Aspirin and clopidogrel
***Platelet count < 50,000 cells/μL, or INR > 1.5 or PTT > 2 times control or use of enoxaparin at doses of > 60 mg per day, or fondaparinux*

Risk Factors for Nosocomial Gastrointestinal Bleeding

Many potential risk factors had strong unadjusted associations with nosocomial gastrointestinal bleeding (Table 1). After including all candidate risk factors in a multivariable model, and retaining only those with a p value < 0.05, several independent risk factors were identified (Table 2). The final model had a c-statistic of 0.78 in the derivation set and 0.79 in the validation set.

Clinical Risk Score and Risk of Bleeding

The risk score for each patient was derived by summing the risk points for each risk factor present (see Table 3). Risk of nosocomial gastrointestinal bleeding increased by more than tenfold from the lowest to highest risk group in both the derivation and validation sets (Fig. 1). In the overall cohort, acid-suppressive medication was utilized in more than 50 % of patients in each risk stratum, including the lowest risk group (Fig. 1).

Table 2. Risk Factors for Nosocomial Gastrointestinal Bleeding in the Derivation Cohort (n=60,578)

Risk factor	Model with all risk factors*	Final model†
	OR (95 % CI)	OR (95 % CI)
Age > 60 years	2.2 (1.4–3.3)	2.2 (1.5–3.2)
Male	1.6 (1.1–2.2)	1.6 (1.2–2.2)
Race		
White	1 (ref)	
Black	1.1 (0.7–1.8)	
Other or unknown	1.1 (0.7–1.7)	
Comorbidities		
Myocardial infarction	0.6 (0.3–1.1)	
Congestive heart failure	1.2 (0.8–1.8)	
Peripheral vascular disease	1.3 (0.8–2.1)	
Cerebrovascular disease	1.3 (0.7–2.3)	
Dementia	0.6 (0.2–1.9)	
Chronic pulmonary disease	0.7 (0.4–1.1)	
Connective tissue disease	1.2 (0.5–2.7)	
Diabetes without complications	1.1 (0.7–1.5)	
Diabetes with complications	1.3 (0.7–2.2)	
Liver disease	2.1 (1.3–3.3)	2.1 (1.3–3.3)
Acute renal failure	1.9 (1.3–2.6)	1.9 (1.3–2.7)
Chronic and unspecified renal failure	1.0 (0.7–1.5)	
Cancer	1.2 (0.8–1.9)	
Metastatic carcinoma	1.1 (0.6–2.1)	
HIV/AIDS	1.3 (0.4–4.2)	
Pneumonia	0.8 (0.5–1.3)	
Sepsis	1.6 (1.02–2.4)	1.6 (1.03–2.4)
Service		
Non-medicine	1 (ref)	
Medicine‡	2.8 (1.8–4.2)	2.7 (1.8–4.1)
In-hospital medications and coagulopathy		
Acid-suppressive medication	0.7 (0.5–0.99)	0.7 (0.5–1.0)
NSAID/COX2 inhibitor	0.8 (0.5–1.3)	
Steroids		
None	1 (ref)	
Low dose§	1.3 (0.7–2.2)	
High dose‖	1.2 (0.8–2.0)	
Prophylactic anticoagulant¶	1.7 (1.2–2.4)	1.7 (1.2–2.4)
Antiplatelet/coagulopathy combinations		
No antiplatelet agent, no coagulopathy	1 (ref)	1 (ref)
Single antiplatelet agent# without coagulopathy	1.3 (0.8–2.2)	1.4 (0.8–2.3)
Dual antiplatelet agents** without coagulopathy	1.8 (0.8–4.1)	1.9 (0.9–4.2)
Coagulopathy†† without antiplatelet agents	2.4 (1.4–3.8)	2.6 (1.6–4.2)
Coagulopathy with single antiplatelet agent	3.1 (1.8–5.3)	3.2 (2.0–5.3)
Coagulopathy with dual antiplatelet agents	3.3 (1.6–7.1)	3.3 (1.6–6.6)

COX2 cyclooxygenase 2; CI confidence interval; HIV/AIDS human immunodeficiency virus/acquired immunodeficiency syndrome; NSAID non-steroidal anti-inflammatory drugs; OR odds ratio

**Risk factors with inadequate outcome numbers (paraplegia/hemiplegia, prior peptic ulcer) were excluded from multivariable models*

†Multivariable logistic regression model retaining only those variables with $p < 0.05$ from model including all risk factors

‡All services other than general surgery, surgical subspecialties, obstetrics and gynecology, neurology, psychiatry

§≤ 200 mg/day of hydrocortisone or the equivalent

‖> 200 mg/day of hydrocortisone or the equivalent

¶Subcutaneous unfractionated heparin and ≤ 60 mg/day of enoxaparin

#Aspirin or clopidogrel

***Aspirin and clopidogrel*

††Platelet count < 50,000 cells/μL, or INR > 1.5 or PTT > 2 times control or use of enoxaparin at doses of >60 mg per day, or fondaparinux

Table 4 shows the rates of nosocomial gastrointestinal bleeding for the entire cohort by risk group, both overall and stratified by acid-suppressive medication status, with accompanying number-needed-to-treat with acid-suppressive medication to prevent one episode of bleeding. The number-needed-to-treat was inversely related to the risk score. Table 5 shows the rates of nosocomial gastrointestinal bleeding at increasing risk score thresholds, with accompanying number-needed-to-treat.

Sensitivity Analyses

After restricting our outcome definition to cases of clinically significant gastrointestinal bleeding (n=159), our final model had a c-statistic of 0.79. After restricting our analysis to admissions without acid-suppressive medication exposure (n=31,629), our final model had a c-statistic of 0.88.

DISCUSSION

Nosocomial gastrointestinal bleeding is an important source of preventable hospital morbidity and mortality. Although effective prophylaxis exists, guidelines have recommended against use in patients outside of the ICU because the average risk of bleeding among such patients is low. Our study addresses an important knowledge gap by identifying independent risk factors for nosocomial gastrointestinal bleeding in these patients specifically. We used these risk factors to develop and validate a predictive model for nosocomial gastrointestinal bleeding with excellent discriminative ability. This model allows for risk stratification of patients using readily available information, and can be used to guide more selective use of acid-suppressive medication in patients outside of the ICU.

Several consistencies between our study and prior studies support the validity of our findings. First, our definition of nosocomial gastrointestinal bleeding is consistent with prior studies, and our outcome incidence is almost identical to that found in non-ventilated ICU patients.[6,14] Furthermore, the risk factors that we identified are similar to those identified in the ICU setting and plausible from a pathophysiologic standpoint.[5–7,14–16] Additionally, similar to our findings, risk in the ICU patient population increases as number of risk factors increases.[5,6,17,18]

Two prior studies have examined risk factors for nosocomial gastrointestinal bleeding in patients outside of the ICU; however, both were small, one was in severely ill patients, and neither presented a clinical risk scoring system.[4,19] Although current guidelines recommend against prophylactic use of acid-suppressive medication outside of the ICU, these guidelines were published more than a decade ago, and were based on expert consensus and the aforementioned small study by Estruch et al. in severely ill

Table 3. Clinical Risk Scoring System for Nosocomial Gastrointestinal Bleeding in Hospitalized Patients Outside of the Intensive Care Unit

Risk factor	Points
Age > 60	2
Male	2
Acute renal failure	2
Liver disease*	2
Sepsis†	2
Prophylactic anticoagulation‡	2
Coagulopathy (based on laboratory values or medications, as defined below)§	3
Medicine Service‖	3

An individual patient's Clinical Risk Score is derived by summing the points for each risk factor present. Risk factors should be viewed as cumulative, and risk score should be updated as risk factors accumulate during a hospitalization

**Any disorder of the liver, including acute and chronic hepatitis (infective or non-infective); acute, subacute, and chronic hepatic failure; chronic liver disease, including hepatic coma, portal hypertension, hepatorenal syndrome and/or other sequelae; hepatic necrosis or infarction; history of liver transplant*

†Includes septicemia due to identified or unidentified organisms, or bacteremia

‡Subcutaneous unfractionated heparin and ≤ 60 mg/day of enoxaparin

§Platelet count < 50,000 cells/μL, or INR > 1.5 or PTT > 2 times control or use of enoxaparin at doses of > 60 mg per day, or fondaparinux

‖ All services other than general surgery, surgical subspecialties, obstetrics and gynecology, neurology, psychiatry

patients.[3,19] Rather than employing a one-size-fits-all approach, our study provides guidance for clinicians in targeting acid-suppressive therapy to those non-ICU-based patients who stand to benefit most, while avoiding the unnecessary cost and risk associated with this therapy in those with extremely low risk of bleeding.

Our numbers-needed-to-treat should be considered in the context of prior studies addressing the risks of acid-suppressive medications in similar patient populations.[20–23] Two

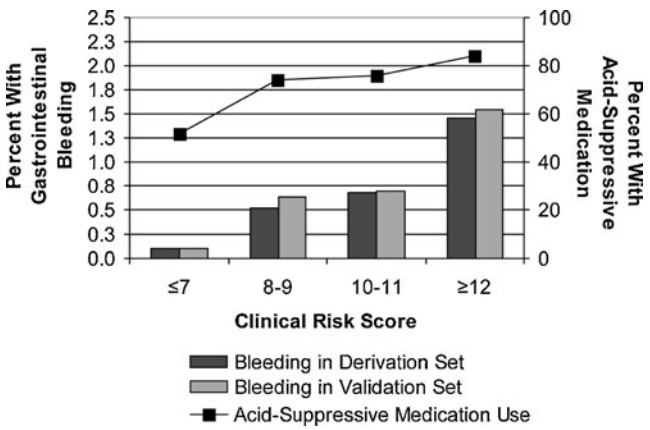

Figure 1. Relationship between clinical risk score and nosocomial gastrointestinal bleeding (*bar graph*) and acid-suppressive medication use (*line graph*). The *bar graph* demonstrates the rate of nosocomial gastrointestinal bleeding by increasing risk group in our cohort, in both the derivation and validation subsets. The *line graph* demonstrates the percent with acid-suppressive medication use in the different risk groups.

Table 4. Nosocomial Gastrointestinal Bleeding According to Clinical Risk Group in the Overall Cohort, and Associated Number-Needed-To-Treat (NNT) with Acid-Suppressive Medication to Prevent One Episode of Nosocomial Gastrointestinal Bleeding (*n*=75,723)

Risk group	Bleeding	No bleeding	Percent with bleeding	NNT
Low risk (≤ 7 points)	58	5,737	0.10	
Without prophylaxis	11	27,447	0.04	
With prophylaxis	47	29,870	0.16	–
Low-medium risk (8–9 points)	47	8,685	0.54	
Without prophylaxis	15	2,218	0.67	
With prophylaxis	32	6,467	0.49	556
High-medium risk (10–11 points)	37	5,427	0.68	
Without prophylaxis	15	1,275	1.16	
With prophylaxis	22	4,152	0.53	159
High risk (≥ 12 points)	61	4,091	1.47	
Without prophylaxis	21	627	3.24	
With prophylaxis	40	3,464	1.14	48

recent studies performed at our medical center identified numbers-needed-to-harm for nosocomial *Clostridium difficile* colitis and hospital-acquired pneumonia of 533 and 111, respectively.[22,23] In our cohort, using a risk score threshold of at least 10 for prophylaxis with acid-suppressive medication would result in a number-needed-to-treat of 95—less than both previously noted numbers-needed-to-harm—while exposing only 13 % of our cohort to acid-suppressive medication.

There are several considerations that should be kept in mind when applying our findings. First, because the risk score includes all risk factors accrued during a hospitalization, it should be viewed as cumulative, and updated periodically. Second, because numbers-needed-to-treat and numbers-needed-to-harm are influenced by the effectiveness and safety of the treatment and the incidence of disease in the unexposed, the specific numbers derived in this cohort should be generalized to other populations with caution. Furthermore, because a

Table 5. Rates of Nosocomial Gastrointestinal Bleeding at Increasing Point Thresholds in the Overall Cohort, and Associated Number-Needed-To-Treat (NNT) with Acid-Suppressive Medication Prophylaxis to Prevent One Episode of Nosocomial Gastrointestinal Bleeding (*n*=75,723)

Risk score	Bleeding	No bleeding	Percent with bleeding	NNT
≥ 6	180	32,709	0.55	
Without prophylaxis	57	8,035	0.70	
With prophylaxis	123	24,674	0.50	500
≥ 8	145	18,203	0.79	
Without prophylaxis	51	4,120	1.22	
With prophylaxis	94	14,083	0.66	179
≥ 10	98	9,518	1.02	
Without prophylaxis	36	1,902	1.86	
With prophylaxis	62	7,616	0.81	95
≥ 12	61	4,091	1.47	
Without prophylaxis	21	627	3.24	
With prophylaxis	40	3,464	1.14	48

spectrum of severity exists even within a given risk factor, clinicians should consider taking into account severity of illness in addition to presence or absence of illness, especially in patients close to the treatment threshold. Additionally, our findings should be validated at other institutions.

Due to the observational nature of our data, we are unable to know what the true rate of bleeding in patients exposed to acid-suppressive medication would have been, had they been unexposed. We attempted to account for this by controlling for acid-suppressive medication use in the model from which our effect estimates were derived. Our finding of a protective effect of acid-suppressive medication similar to that seen in randomized controlled trials[1] suggests adequate control of such confounding. However, given the observational nature of our data, the possibility of residual confounding and bias still remains. To further address this limitation, we assessed performance of our model in only those patients unexposed to acid-suppressive medication. Our model had even greater discriminatory ability in this subgroup. Given the infrequency of nosocomial gastrointestinal bleeding, an adequately powered randomized controlled trial of acid-suppressive medication would require a prohibitively large sample size (> 25,000 patients), and is unlikely to occur. Thus, despite the limitations of our observational data, we believe our results currently represent the best data available to guide clinical practice.

We were unable to obtain a number-needed-to-treat with acid-suppressive medication in our lowest risk group, because the risk of gastrointestinal bleeding was higher in patients exposed to acid-suppressive medication than patients unexposed. Since it is physiologically implausible that acid-suppressive medication promotes gastrointestinal bleeding, we believe this observation likely represents residual confounding by indication in the lowest risk group. Given the exceedingly low incidence of bleeding in this group, even if we assume a 50 % risk reduction with acid-suppressive medication (higher than the 30 % reduction seen overall), the number-needed-to-treat would still be greater than 1,000.

Additionally, due to a low rate of use of histamine-2 receptor antagonists, we chose to group proton-pump inhibitors and histamine-2 receptor antagonists into a single exposure variable. We performed a sensitivity analysis in which we used separate terms for proton-pump inhibitors and histamine-2 receptor antagonists in our models. Our findings were unchanged, and the effect estimates for the association between each class of medication and nosocomial gastrointestinal bleeding were very similar.

Another limitation relates to our lack of outpatient records. We could not identify which patients had preexisting gastrointestinal conditions, nor could we differentiate acid-suppressive medication initiated in the hospital from outpatient medication continued in hospital. Future studies should examine whether duration of use modifies the relationship between acid-suppressive medication and gastrointestinal bleeding.

In conclusion, in a large cohort of non-critically ill hospitalized patients, we identified several independent risk factors for nosocomial gastrointestinal bleeding which, when incorporated into a risk scoring system, allowed reproducible classification of patients according to their bleeding risk. The scoring system allows identification of subsets of patients in whom the risk of nosocomial gastrointestinal bleeding may be high enough to warrant the prophylactic use of acid-suppressive medication in the absence of other indications for use. With further validation at other medical centers, this scoring system may help clinicians individualize the decision to prescribe acid suppressive medication as prophylaxis.

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