CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

More Favorable Outcomes with Peptic Ulcer Bleeding Due to *Helicobacter Pylori*

Rebecca D. Chason,[a] Joan S. Reisch, PhD,[b] Don C. Rockey, MD[c]

[a]Division of Digestive and Liver Diseases, Department of Internal Medicine, [b]Division of Biostatistics, Department of Clinical Sciences, University of Texas Southwestern Medical Center and Parkland Memorial Hospital, Dallas; [c]Department of Internal Medicine, Medical University of South Carolina, Charleston.

ABSTRACT

BACKGROUND: Acute upper gastrointestinal bleeding is a common complication of peptic ulcer disease, often caused by *Helicobacter pylori* and nonsteroidal anti-inflammatory drug (NSAID) use. The purpose of this study was to determine whether the cause and biologic behavior of ulcers associated with acute upper gastrointestinal bleeding might lead to divergent patient outcomes.

METHODS: In this Institutional Review Board-approved study, we compared clinical features and outcomes of patients with acute upper gastrointestinal bleeding due to ulcers categorized into 4 groups: *Helicobacter pylori* positive or negative combined with NSAID usage positive or negative. Likelihood chi-squared analyses were utilized for group comparisons and stepwise multiple logistic regression models were utilized to determine which factors were related to bleeding outcomes.

RESULTS: Of 2242 patients with upper gastrointestinal bleeding, 575 (26%) had gastroduodenal ulcer disease, and of those with appropriate diagnostic testing, approximately half (228, 10% overall) had evidence of *Helicobacter pylori* infection and half (216, 10% overall) had no evidence of *Helicobacter pylori* infection. Patients without *Helicobacter pylori* infection had significantly more comorbid conditions than those with *Helicobacter pylori* and higher Charlson Index comorbidity scores (2.6 ± 2.6 [mean and SD] vs 1.9 ± 2.3, $P = .003$). Hospital length of stay was significantly longer for *Helicobacter pylori*-negative patients (mean 11.4 ± 21.7 vs 6 ± 8.5 days and median 5.5 vs 3 days, $P < .001$ and $< .001$, respectively). Rebleeding events within 30 days were more frequent in *Helicobacter pylori*-negative patients than *Helicobacter pylori*-positive patients (11% vs 5%, $P = .009$). Rebleeding was most frequent in patients without *Helicobacter pylori* and with no reported use of NSAIDS (18%, $P = .01$).

CONCLUSIONS: *Helicobacter pylori*-negative ulcers were associated with poorer outcomes regardless of use of NSAIDs. Patients with ulcers negative for *Helicobacter pylori* and no history of NSAID use had the worst outcomes and had more severe systemic disease.

 • *The American Journal of Medicine (2013) 126, 811-818*

KEYWORDS: *Helicobacter pylori*; Hemorrhage; Nonsteroidal anti-inflammatory drugs; Peptic ulcer disease; Upper gastrointestinal

Acute upper gastrointestinal bleeding is a common medical condition, often requiring hospital admission, that affects approximately 400,000 individuals per year in the US.[1,2] Peptic ulcer disease is currently the most common cause of upper gastrointestinal bleeding, accounting for an estimated 25%-30% of all cases.[2-6] The 2 major underlying causes of peptic ulcer disease (defined as duodenal or gastric ulcer) are *Helicobacter pylori* infection and nonsteroidal

Funding: None.

Conflict of Interest: None.

Authorship: RDC: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. JSR: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. DCR: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Requests for reprints should be addressed to Don C. Rockey, MD, Department of Internal Medicine, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 803, MSC 623, Charleston, SC 29425.

E-mail address: rockey@musc.edu

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2013.02.025

anti-inflammatory drug (NSAID) use.[3,5-17] Recent studies have suggested that some peptic ulcers are unrelated to either NSAID use or *Helicobacter pylori* infection and have been termed "idiopathic ulcers."[7,17-20]

Helicobacter pylori are gram-negative, flagellated bacteria that colonize in the gastric mucosa. In the US, the reported prevalence of *Helicobacter pylori* varies from <10% to nearly 80%, with the highest rates found in patients from lower socioeconomic living conditions.[21,22] Clinically, infection presents most often as peptic ulcer disease; however, it should be noted that only 20% of infected individuals develop peptic ulcer disease and only a quarter of those develop ulcer complications such as upper gastrointestinal bleeding.[22]

NSAIDs, including aspirin, are widely used medications for analgesia, as anti-inflammatory agents, and for their antiplatelet effects.[11] Although their use is often underreported, it is estimated that over 60 million Americans take them on a routine basis. Further, they are one of the most frequently used medications worldwide.[10,11] NSAIDs have been implicated in the mucosal injury of both the upper and lower gastrointestinal tract, where both topical and systemic effects may lead to cellular injury, ulceration, and bleeding.[10,11]

Based on our own clinical experience and previous data suggesting that the underlying etiology of peptic ulcers may play a role in their clinical course,[5-7,15] we hypothesized that patients with *Helicobacter pylori*-negative ulcers may have different outcomes than those positive for *Helicobacter pylori*. Therefore, the purpose of this study was to determine whether the inherent differences in the cause and biologic behavior of ulcers associated with acute upper gastrointestinal bleeding may be associated with different outcomes.

CLINICAL SIGNIFICANCE

- *Helicobacter pylori*-negative ulcers are associated with poorer outcomes regardless of use of nonsteroidal anti-inflammatory drugs.
- Peptic ulcer rebleeding is less likely in women and patients positive for *Helicobacter pylori*.
- Patients with ulcer bleeding should have early and aggressive testing for *Helicobacter pylori* to help triage optimal care.

METHODS

This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board and met all criteria for good clinical research.[23] This was a retrospective analysis of all patients who presented to Parkland Memorial Hospital (a University of Texas Southwestern teaching hospital, Dallas, Tex) between January 1, 2006 and February 27, 2012 with acute upper gastrointestinal bleeding, who underwent diagnostic or therapeutic endoscopy by a dedicated gastroenterologist within 24 hours of admission, were found to have peptic ulcer disease as the bleed etiology, and were tested for *Helicobacter pylori*. Patients with gastrointestinal bleeding were identified and data pertaining to their hospital admission were entered prospectively into our institution's Gastrointestinal Health Care registry (Microsoft Access, Microsoft Corporation, Redmond, Wash). Demographic data included age, sex, and ethnicity, as well as clinical data including symptoms, medical and social history, medications, admission physical examination findings, laboratory data including *Helicobacter pylori* diagnostic testing, and endoscopic procedure findings (diagnosis, stigmata of recent or active bleeding, and therapeutic intervention). Thirty-day rebleeding events and 30-day mortality also were collected. Patients with documented *Helicobacter pylori* diagnostic testing (see below) were initially grouped and compared by *Helicobacter pylori* diagnosis (positive or negative) and then were subdivided and compared by use of any NSAID (positive or negative). Ulcers associated with malignant lesions, those with equivocal diagnostic results, or those without diagnostic testing were excluded from analysis.

Definitions

Acute upper gastrointestinal bleeding was defined as bleeding proximal to the ligament of Treitz[1] presenting as reported or witnessed hematemesis, melena, or hematochezia within 7 days of admission, with a decrease in hematocrit from baseline ≥4 points.[24]

NSAID use was defined as use of either aspirin or any known NSAID more than 4 times in the month before admission. *Helicobacter pylori* status was determined by employing one or more of the following techniques: 1) serological testing for *Helicobacter pylori antibodies*, 2) stool samples for antigens, 3) random biopsies taken during endoscopy, and 4) the *Campylobacter*-like organism test or Rapid urease test. The majority of peptic ulcer patients had more than one diagnostic test performed. If any of the tests were positive for *Helicobacter pylori*, the patient was presumed to have a *Helicobacter pylori*-mediated ulcer. Thus, all diagnostic tests performed on any patient had to be negative for the patient to be classified as "*Helicobacter pylori* negative." Patients with equivocal results for serological testing or evidence of malignancy postbiopsy were excluded from analysis.

By design, we differentiated patients into the following 4 groups:

1. *Helicobacter pylori* negative/NSAID negative (HP−/NSAID−) (also idiopathic),
2. *Helicobacter pylori* negative/NSAID positive (HP−/NSAID+),
3. *Helicobacter pylori* positive/NSAID negative (HP+/NSAID−),
4. *Helicobacter pylori* positive/NSAID positive (HP+/NSAID+).

Comorbid conditions collected were as follows and included: diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, myocardial infarction, asthma, chronic obstructive pulmonary disease, end-stage renal disease, cerebrovascular accident, peptic ulcer disease, gastroesophageal reflux disease, cirrhosis, neoplasia, acquired immune deficiency syndrome, and hepatitis B or C (or both).

Endoscopic therapy was performed as per the standard of care for ulcers with stigmata of bleeding.[1,2,25] Endoscopic therapies include epinephrine injection, thermal coagulation, and hemoclip placement.[1,2] The standard practice at our institution is to administer combination therapy, which may include injection of epinephrine and thermal coagulation, injection and hemoclip placement, or injection with thermal coagulation and hemoclip placement to achieve endoscopic hemostasis.

Causes of death for patients were classified into 8 categories as follows: gastrointestinal bleeding, cardio or respiratory failure, renal failure, liver failure or cirrhosis complications, sepsis, multiorgan dysfunction syndrome, terminal malignancy, or other. The study team adjudicates the cause of death in a blinded fashion; death was considered to be due to bleeding when the patient either died while actively bleeding or when the bleeding event led to a subsequent event that caused death (eg, surgery).

Statistical Analysis

Analyses for this research project were carried out utilizing SAS, version 9.2 (SAS Institute Inc., Cary, NC). Data were compiled for 444 subjects. Of those, 216 patients were *Helicobacter pylori* negative and 228 were *Helicobacter pylori* positive. Multiple demographic and clinical variables were examined, including age; sex; ethnicity; aspirin and NSAID use; smoking and alcohol use; comorbidities; Charlson Index; presence of hematemesis, melena or hematochezia; vital signs; and multiple laboratory values. Subjects were categorized into 4 groups: *Helicobacter pylori* positive or negative combined with NSAID usage positive or negative.

Categorical data items were summarized utilizing frequency counts and percentages while means and SDs were calculated for the numerical measurements. In order to gain insight for the multivariate analyses, the individual measurements were each compared, grouped according to the outcome measure. Likelihood chi-squared analyses were utilized for group comparisons of each of the categorical measurements and one-way analysis of variance for the numerical measurements.

Stepwise multiple logistic regression models were utilized to determine which of the demographic and clinical risk factors were statistically related to the bleeding outcome. Of the 444 subjects, 429 (96.6%) had complete data. The model entry criteria were selected at 5%. The Hosmer Lemeshow technique was utilized to assess the model fit.

RESULTS

Approximately 25% of patients with upper gastrointestinal bleeding had ulcer disease, and of those with appropriate diagnostic testing, approximately half had evidence of *Helicobacter pylori* infection and half did not (**Figure**). Of those positive for *Helicobacter pylori*, 125 (55%) reported use of NSAIDS, while of those negative for *Helicobacter pylori*, 143 (66%) reported use of NSAIDS ($P = .018$) (**Supplemental Table 1**). The epidemiology of ulcers was notably different: more men than women were *Helicobacter pylori* positive, and patients of Hispanic or black ethnicity were significantly more likely to be *Helicobacter pylori* positive than white patients (**Table 1**). Further, patients without *Helicobacter pylori* infection had significantly more comorbid conditions and higher Charlson Index comorbidity scores[26]—with and without adjustment for age—than those with *Helicobacter pylori* ($P = .001$) (**Table 1**).

Clinical features suggested that patients without *Helicobacter pylori* had more severe bleeding than those with *Helicobacter pylori*, including more prominent hematochezia (12 [16%], $P = .01$) (**Table 2**), slightly lower blood pressure (in HP−/NSAID+ patients), and more frequent admission to the intensive care unit (**Table 2**). Pre-endoscopy Rockall and American Society of Anesthesiologists (ASA) scores also were higher in *Helicobacter pylori*-negative patients compared with positive patients (**Supplemental Table 1**). Blood urea nitrogen levels were slightly higher in *Helicobacter pylori*-negative patients (39 ± 33 vs 34 ± 27, $P = .05$), consistent with more substantial bleeding (**Supplemental Table 1**).

Helicobacter pylori-positive ulcers were located in the duodenum more often than *Helicobacter pylori*-negative ulcers (43% vs 30%, $P = .016$) (**Table 3**). Additionally, patients with *Helicobacter pylori*-negative ulcers more frequently had >3 ulcers compared with those that were *Helicobacter pylori* positive. However, there did not appear to be differences in the frequency of stigmata of recent bleeding or need for endoscopic therapy. All patients were treated with an intravenous or oral proton pump inhibitor during their hospital stay and discharged with prescriptions for proton pump inhibitors.

Duodenal ulcers were more often *Helicobacter pylori* positive than gastric ulcers (60% vs 47%, $P = .014$) (**Supplemental Table 2**). Ulcer characteristics were similar in the 2 locations; however, duodenal ulcers appeared to have a slightly higher frequency of having stigmata of recent bleeding and need for endoscopic therapy, although these differences were not statistically significantly different.

The length of hospital stay was significantly longer for *Helicobacter pylori*-negative patients (**Table 4**, **Supplemental Table 1**). HP−/NSAID− patients had the longest median length of stay (7 days), and HP+/NSAID+ and HP+/NSAID− stayed the shortest amount of time (3 days). In addition, rebleeding events within 30 days were more frequent in *Helicobacter pylori*-negative patients ($P = .01$) (**Table 4**, **Supplemental Table 1**); HP−/NSAID− ulcer

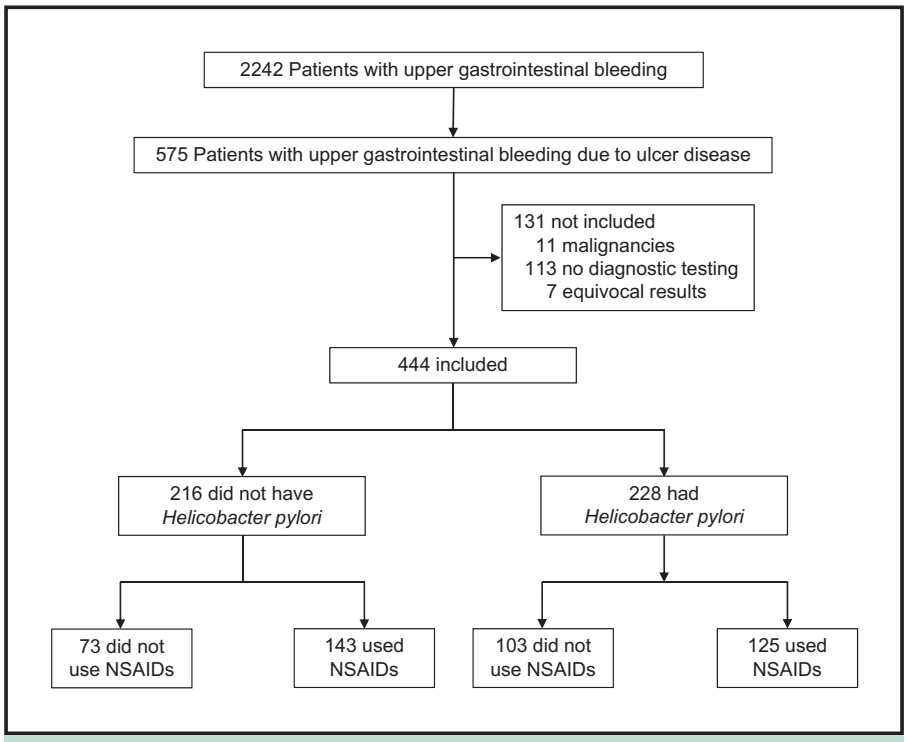

Figure Patient groups. The numbers of patients in the 4 different groups, as defined by *Helicobacter pylori* status and nonsteroidal anti-inflammatory drug (NSAID) use, is shown.

patients had the highest rate of rebleeding at 18%. Mortality at 30 days was similar for all 4 groups, with the most common cause of death being multi-organ dysfunction syndrome and respiratory/cardiac failure. There were 3 deaths specifically due to gastrointestinal bleeding; 2 of which were in *Helicobacter pylori*-negative patients.

Regression analysis to evaluate predictors of re-bleeding revealed that being *Helicobacter pylori* positive

Table 1 Patient Characteristics

	H. pylori (−) n = 216		H. pylori (+) n = 228		
	NSAID (−) n = 73 n, Mean (%, SD)	NSAID (+) n = 143 n, Mean (%, SD)	NSAID (−) n = 103 n, Mean (%, SD)	NSAID (+) n = 125 n, Mean (%, SD)	*P* Value
Age in years	53 ± 14	55 ± 13	51 ± 13	55 ± 14	.077
Range	23–88	18–84	20–85	22–93	
Sex					.001
Female	27 (37%)	58 (41%)	18 (17%)	38 (30%)	
Male	46 (63%)	85 (59%)	85 (83%)	87 (70%)	
Ethnicity					<.0001
Hispanic	18 (25%)	32 (22%)	41 (40%)	54 (43%)	
African American	23 (32%)	41 (29%)	42 (41%)	50 (40%)	
Caucasian	27 (39%)	59 (41%)	17 (17%)	15 (12%)	
Other*	5 (7%)	11 (8%)	3 (3%)	6 (5%)	
Smoking	31 (42%)	90 (63%)	53 (51%)	71 (57%)	.030
Alcohol	45 (62%)	74 (52%)	60 (58%)	83 (66%)	.103
Charlson Index	2.4 ± 2.7	2.7 ± 2.6	1.9 ± 2.4	1.9 ± 2.3	.021
Charlson Age-adjusted Index	3.2 ± 3.0	3.7 ± 3.2	2.5 ± 2.9	2.7 ± 2.9	.006
Number of comorbidities	1.9 ± 1.3	2.4 ± 1.7	1.7 ± 1.5	1.9 ± 1.5	.003

NSAID = nonsteroidal anti-inflammatory drug.
*Other ethnicities included Asian/Pacific Islander/East Indian and Native American.

Table 2 Clinical Features

	H. pylori (−) n = 216		H. pylori (+) n = 228		
	NSAID (−) n = 73 n, Mean (%, SD)	NSAID (+) n = 143 n, Mean (%, SD)	NSAID (−) n = 103 n, Mean (%, SD)	NSAID (+) n = 125 n, Mean (%, SD)	*P* Value
Hematemesis	44 (60%)	62 (43%)	51 (50%)	61 (49%)	.134
Melena	43 (59%)	118 (83%)	85 (83%)	97 (78%)	.001
Hematochezia	12 (16%)	16 (11%)	10 (10%)	4 (3%)	.010
ICU at admission	24 (33%)	51 (36%)	22 (21%)	28 (22%)	.027
Admission vital signs					
Systolic blood pressure	125 ± 29	122 ± 28	127 ± 25	126 ± 22	.471
Diastolic blood pressure	70 ± 20	67 ± 16	74 ± 17	71 ± 16	.022
Pulse	93 ± 20	92 ± 23	94 ± 21	93 ± 20	.945
Rockall (ER)	2.9 ± 1.3	2.9 ± 1.2	2.4 ± 1.4	2.6 ± 1.2	.012
ASA score	2.4 ± 0.7	2.5 ± 0.7	2.2 ± 0.6	2.3 ± 0.6	<.0001
Admission laboratory values					
Hematocrit (%)	30.0 ± 8.8	27.6 ± 8.6	29.7 ± 9.4	28.0 ± 8.4	.122
Platelets ($\times 10^9$/L)	261 ± 147	254 ± 126	233 ± 99	251 ± 113	.434
INR	1.3 ± 0.6	1.5 ± 1.4	1.2 ± 0.4	1.2 ± 0.4	.047
BUN (mg/dL)	36.4 ± 33.3	39.7 ± 33.0	30.8 ± 27.9	36.4 ± 25.8	.153

ASA = American Society of Anesthesiologists; BUN = blood urea nitrogen; ICU = intensive care unit; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

was associated with a decreased likelihood of rebleeding (**Table 5**). Additionally, as expected, endoscopic therapy was associated with an increased risk of rebleeding, although combination therapy of all types reduced the risk of rebleeding compared with single-modality therapy.

DISCUSSION

In this study, we have documented a number of demographic and clinical differences in patients with peptic ulcer disease, depending on *Helicobacter pylori* and NSAID status. We also have shown that patients with *Helicobacter pylori*-negative ulcers appear to have a generally greater degree of morbidity than those with *Helicobacter pylori*-positive ulcers. Patients with *Helicobacter pylori*-negative ulcers also exhibited differences in certain outcomes such as a longer hospital stay and more frequent rebleeding events at 30 days. Finally, the data suggest that *Helicobacter pylori* infection status may be more critical than use of NSAIDs for predicting poorer outcomes.

We found that female sex and *Helicobacter pylori* infection were negative predictors of rebleeding. This is consistent with other data showing that patients positive for *Helicobacter pylori* are typically treated with antibiotics and cured, thus decreasing their rate of rebleeding.[8,27,28] Endoscopic therapy was a significant positive predictor of rebleeding. This is consistent with the concept that high-risk lesions typically are selected for endoscopic therapy.[1,2,25] Consistent with previous data, our findings suggest that combination therapy is more effective than use of monotherapy for treatment of ulcers.

We identified 73 patients with no reported history of NSAID use and negative diagnostic results for *Helicobacter pylori,* otherwise known as idiopathic ulcers. Bleeding peptic ulcers may interfere with *Helicobacter pylori* diagnostic testing, therefore false negatives for *Helicobacter pylori* must be considered as a possible etiology, as well as unreported use of NSAIDs and aspirin.[13,18,20] Causes of true idiopathic ulcers include older age, tobacco use, Zolinger Ellison Syndrome, systemic mastocytosis, or other underlying systemic diseases.[17,20] Of the 73 patients identified with idiopathic ulcers, the presence of these conditions was not found or is unknown. This group had high Charlson scores and a large number of comorbidities, as well as high ASA and ER Rockall scores, which is consistent with underlying conditions likely contributing to poorer outcomes. This group had the longest median length of hospital stay (7 days) and greatest incidence of rebleeding (18%). Of note, differences in mortality were not observed among the 4 groups, perhaps related to our sample size. We speculate that inclusion of very large numbers of patients may demonstrate differences in mortality. Nonetheless, our findings are consistent with other literature examining bleeding idiopathic peptic ulcers that have reported more adverse outcomes for this group.[7,20,29]

There is a robust body of literature examining clinical features and outcomes in patients with ulcer bleeding from Asian, European, and South American populations.[3,8,9,11-16,18,29-31] However, there are very few data on this subject in US populations. Conclusions drawn about the etiology, incidence, severity, treatment, and outcomes of peptic ulcer bleeding in previous studies may or may not be generalizable to an American population due to variations in

Table 3 Ulcer Characteristics and Treatment

	H. pylori (−) n = 216		H. pylori (+) n = 228		
	NSAID (−) n = 73 n (%)	NSAID (+) n = 143 n (%)	NSAID (−) n = 103 n (%)	NSAID (+) n = 125 n (%)	*P* Value
Location of ulcers					.016
Stomach	46/73 (63%)	83/143 (58%)	43/103 (42%)	73/125 (58%)	
Duodenum	22/73 (30%)	44/143 (31%)	52/103 (50%)	46/125 (37%)	
Stomach + duodenum	5/73 (7%)	16/143 (11%)	8/103 (8%)	6/125 (5%)	
Number of ulcers					.006
1	48/73 (66%)	77/143 (54%)	71/103 (69%)	80/125 (64%)	
2	7/73 (10%)	30/143 (21%)	20/103 (19%)	27/125 (22%)	
3	3/73 (4%)	10/143 (7%)	7/103 (7%)	8/125 (6%)	
>3	15/73 (21%)	26/143 (18%)	5/103 (5%)	10/125 (8%)	
Stigmata present	27/73 (37%)	61/143 (43%)	40/103 (39%)	49/125 (39%)	.853
Active bleeding	10/27 (37%)	20/61 (33%)	14/40 (35%)	10/49 (21%)	
Visible vessel	9/27 (33%)	28/61 (46%)	20/40 (50%)	31/49 (63%)	
Adherent clot	8/27 (30%)	13/61 (21%)	6/40 (15%)	8/49 (26%)	
Stigmata absent	46/73 (63%)	82/143 (57%)	63/103 (61%)	76/125 (61%)	
Pigmented spot	8/46 (17%)	18/82 (22%)	12/63 (19%)	6/76 (8%)	
Clean base	38/46 (83%)	64/82 (78%)	51/63 (81%)	70/76 (92%)	
Endoscopic therapy	26/73 (36%)	60/143 (42%)	42/103 (41%)	50/125 (40%)	.840
Epinephrine injection	7/26 (27%)	5/60 (8%)	3/42 (7%)	4/50 (8%)	
Thermal coagulation	1/26 (4%)	3/60 (5%)	3/42 (7%)	4/50 (8%)	
Hemoclips	5/26 (19%)	5/60 (8%)	0/42 (0%)	6/50 (12%)	
Combination therapy	13/26 (50%)	47/60 (79%)	36/42 (86%)	36/50 (72%)	

NSAID = nonsteroidal anti-inflammatory drug.

the epidemiology of *Helicobacter pylori* and physician practice patterns worldwide.[21,22,32] A Greek study comparing bleeding duodenal ulcers with and without *Helicobacter pylori* shows those patients not infected with *Helicobacter pylori* to have more severe index bleeding and higher rebleeding rates.[19] Results from Asian studies have shown true idiopathic ulcers to be at high risk of recurrent bleeding and mortality.[7,12] Thus, our findings are in

Table 4 Outcomes

	H. pylori (−) n = 216		H. pylori (+) n = 228		
	NSAID (−) n = 73 n, Mean (%, SD)	NSAID (+) n = 143 n, Mean (%, SD)	NSAID (−) n = 103 n, Mean (%, SD)	NSAID (+) n = 125 n, Mean (%, SD)	*P* Value
RBC transfused	47 (64%)	100 (70%)	68 (66%)	76 (61%)	.472
Units	4.5 ± 5.1	4.2 ± 3.4	3.6 ± 3.4	3.8 ± 2.5	.543
Platelets transfused	2 (3%)	3 (2%)	1 (1%)	2 (2%)	.827
Units	2.0 ± 1.4	1.3 ± 0.6	6.0	1.0 ± 0.0	.026
FFP transfused	9 (12%)	11 (8%)	4 (4%)	6 (5%)	.136
Units	4.0 ± 3.3	2.6 ± 1.2	3.5 ± 2.4	4.8 ± 3.8	.427
ICU transfer	6 (8%)	8 (6%)	4 (4%)	6 (5%)	.659
Mechanical ventilation	7 (10%)	7 (5%)	1 (1%)	7 (7%)	.049
Angiography	2 (3%)	0 (0%)	2 (2%)	1 (1%)	.165
Surgery	5 (7%)	4 (3%)	3 (3%)	1 (1%)	.128
Length of stay (mean, days)	11.7 ± 12.5	11.3 ± 25.2	6.5 ± 9.8	5.6 ± 7.4	.007
Length of stay (median, days)	7 (1, 53)	5 (1, 238)	3 (1, 62)	3 (1, 41)	<.0001
Rebleed within 30 days	13 (18%)	12 (8%)	4 (4%)	7 (6%)	.010
Mortality within 30 days	4 (6%)	5 (4%)	4 (4%)	4 (3%)	.881

FFP = fresh frozen plasma; ICU = intensive care unit; NSAID = nonsteroidal anti-inflammatory drug; RBC = red blood cells.

Table 5 Variables Associated with Rebleeding

Variable	Odds Ratio	95% Confidence Interval
Sex (female)	0.282	0.106-0.747
Helicobacter pylori positive	0.393	0.178-0.868
Hematochezia	2.593	1.029-6.536
Number of comorbidities	1.500	1.189-1.892
Therapy—epinephrine injection only	6.997	1.989-24.609
Therapy—thermal coagulation only	6.840	1.419-32.963
Therapy—combination	2.439	1.076-5.518

The table includes data from a logistic regression analysis designed to evaluate factors associated with rebleeding; the Hosmer Lemeshow test for the goodness of model fit indicated a reasonable fit with chi-squared = 8.13 ($df = 8$) and $P = .421$.

agreement with these studies, but differ from a German study that reported similar rebleeding rates in peptic ulcers with and without *Helicobacter pylori*.[33] Thus, an important advantage with the current study is the analysis of a large and heterogeneous US population; implicit in this point is that the data are likely to be generalizable to Western populations.

We recognize strengths and limitations of our study. First, our study was single centered, and this could limit its generalizability. However, we would emphasize that we examined a very heterogeneous population of patient ethnicities, and this point is likely a strength. Second, as highlighted above, our sample size may not have been large enough to detect differences in mortality, and we cannot exclude the possibility that mortality is increased in patients with *Helicobacter pylori* and NSAID negative ulcers. Next, a number of patients were excluded due to lack of diagnostic testing for *Helicobacter pylori.* Although data were collected prospectively, we did not prescribe specific *Helicobacter pylori* diagnostic testing. While we doubt selection bias on this basis, we cannot exclude the possibility that patients in one group or the other were selectively not evaluated.

In summary, our findings indicate that patients with *Helicobacter pylori*-mediated ulcers have different clinical features and outcomes than patients with NSAID or idiopathic ulcers. Specifically, patients with *Helicobacter pylori* have a more benign clinical course and more favorable outcomes with peptic ulcer bleeding. These findings are significant because they suggest that care for patients with upper gastrointestinal bleeding due to peptic ulcer disease may be triaged, in part, by ascertainment of *Helicobacter pylori* status. We suggest that all ulcer disease patients have early and aggressive testing for *Helicobacter pylori*. Patients with *Helicobacter pylori* can be started on standard-of-care triple antibiotic therapy to facilitate ulcer healing, thus decreasing recurrent ulcer complications.[2,8] *Helicobacter pylori*-negative ulcers are associated with poor outcomes regardless of use of NSAIDs and therefore, patients without *Helicobacter pylori* should be supported medically as appropriate to improve their underlying medical status, and should be treated as aggressively as possible with proton pump inhibitors.

References

1. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med*. 2008;359(9):928-937.
2. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107(3):345-360.
3. Sung JJ. Management of nonsteroidal anti-inflammatory drug-related peptic ulcer bleeding. *Am J Med*. 2001;110(1A):29S-32S.
4. Balderas V, Bhore R, Lara LF, Spesivtseva J, Rockey DC. The hematocrit level in upper gastrointestinal hemorrhage: safety of endoscopy and outcomes. *Am J Med*. 2011;124(10):970-976.
5. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. *Digestion*. 2011;84(2):102-113.
6. van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol*. 2008;22(2):209-224.
7. Wong GL, Wong VW, Chan Y, et al. High incidence of mortality and recurrent bleeding in patients with *Helicobacter pylori*-negative idiopathic bleeding ulcers. *Gastroenterology*. 2009;137(2):525-531.
8. Gisbert JP, Calvet X, Cosme A, et al. Long-term follow-up of 1,000 patients cured of *Helicobacter pylori* infection following an episode of peptic ulcer bleeding. *Am J Gastroenterol*. 2012;107(8):1197-1204.
9. Fujinami H, Kudo T, Hosokawsa A, et al. A study of the changes in the cause of peptic ulcer bleeding. *World J Gastrointest Endosc*. 2012;4(7):323-327.
10. Lee I, Cryer B. Epidemiology and role of nonsteroidal antiinflammatory drugs in causing gastrointestinal bleeding. *Gastrointest Endosc Clin N Am*. 2011;21(4):597-612.
11. Sostres C, Lanas A. Epidemiology and demographics of upper gastrointestinal bleeding: prevalence, incidence, and mortality. *Gastrointest Endosc Clin N Am*. 2011;21(4):567-581.
12. Liu NJ, Lee CS, Tang JH, et al. Outcomes of bleeding peptic ulcers: a prospective study. *J Gastroenterol Hepatol*. 2008;23(8 Pt 2): e340-e347.
13. Ootani H, Iwakiri R, Shimoda R, et al. Role of Helicobacter pylori infection and nonsteroidal anti-inflammatory drug use in bleeding peptic ulcers in Japan. *J Gastroenterol*. 2006;41(1):41-46.
14. Zapata-Colindres JC, Zepeda-Gomez S, Montano-Loza A, Vazquez-Ballesteros E, de Jesus Villalobos J, Valdovinos-Andraca F. The association of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs in peptic ulcer disease. *Can J Gastroenterol*. 2006;20(4):277-280.
15. Chan HL, Wu JC, Chan FK, et al. Is non-*Helicobacter pylori*, non-NSAID peptic ulcer a common cause of upper GI bleeding? A prospective study of 977 patients. *Gastrointest Endosc*. 2001;53(4): 438-442.
16. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. *Aliment Pharmacol Ther*. 2009;29(9):938-946.
17. Boltin D, Halpern M, Levi Z, et al. Gastric mucin expression in *Helicobacter pylori*-related, nonsteroidal anti-inflammatory drug-related and idiopathic ulcers. *World J Gastroenterol*. 2012;18(33):4597-4603.
18. Gisbert JP, Calvet X. Review article: *Helicobacter pylori*-negative duodenal ulcer disease. *Aliment Pharmacol Ther*. 2009;30(8):791-815.
19. Adamopoulos AB, Efstathiou SP, Tsioulos DI, et al. Bleeding duodenal ulcer: comparison between *Helicobacter pylori* positive and *Helicobacter pylori* negative bleeders. *Dig Liver Dis*. 2004;36(1): 13-20.
20. Niv Y. *H. pylori*/NSAID-negative peptic ulcer—the mucin theory. *Med Hypotheses*. 2010;75(5):433-435.
21. Goh KL, Chan WK, Shiota S, Yamaoka Y. Epidemiology of *Helicobacter pylori* infection and public health implications. *Helicobacter*. 2011;16(Suppl 1):1-9.
22. Malaty HM. Epidemiology of *Helicobacter pylori* infection. *Best Pract Res Clin Gastroenterol*. 2007;21(2):205-214.
23. Tognoni G. The new Helsinki declaration [Italian]. *Assist Inferm Ric*. 2009;28(1):49-51.

24. Rockey DC. Gastrointestinal bleeding. *Gastroenterol Clin North Am*. 2005;34(4):581-588.
25. Barkun AN, Martel M, Toubouti Y, Rahme E, Bardou M. Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses. *Gastrointest Endosc*. 2009;69(4):786-799.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
27. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report. *Gut*. 2012;61(5):646-664.
28. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut*. 2010;59(8):1143-1153.
29. Wong GL, Au KW, Lo AO, et al. Gastroprotective therapy does not improve outcomes of patients with Helicobacter pylori-negative idiopathic bleeding ulcers. *Clin Gastroenterol Hepatol*. 2012;10(10):1124-1129.
30. Kamada T, Hata J, Kusunoki H, et al. Endoscopic characteristics and *Helicobacter pylori* infection in NSAID-associated gastric ulcer. *J Gastroenterol Hepatol*. 2006;21(1 Pt 1):98-102.
31. Sung JJ, Tsoi KK, Ma TK, Yung MY, Lau JY, Chiu PW. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol*. 2010;105(1):84-89.
32. Tang SJ, Lee SY, Hynan LS, et al. Endoscopic hemostasis in nonvariceal upper gastrointestinal bleeding: comparison of physician practice in the East and the West. *Dig Dis Sci*. 2009;54(11):2418-2426.
33. Schilling D, Demel A, Nusse T, Weidmann E, Riemann JF. *Helicobacter pylori* infection does not affect the early rebleeding rate in patients with peptic ulcer bleeding after successful endoscopic hemostasis: a prospective single-center trial. *Endoscopy*. 2003;35(5):393-396.

Supplemental Table 1 Comparison of Groups Based on *Helicobacter pylori* Status

	H. pylori (−) n = 216 n, Mean (%, SD)	H. pylori (+) n = 228 n, Mean (%, SD)	*P* Value
NSAIDS or aspirin	143 (66%)	125 (55%)	.018
Charlson Index	2.6 ± 2.6	1.9 ± 2.3	.003
Charlson Age-adjusted Index	3.5 ± 3.1	2.6 ± 2.9	.001
Number of comorbidities	2.2 ± 1.6	1.8 ± 1.5	.006
ICU at admission	75 (35%)	50 (22%)	.003
Admission vitals			
Systolic blood pressure	123 ± 28	126 ± 28	.237
Diastolic blood pressure	68 ± 18	72 ± 16	.012
Pulse	93 ± 22	93 ± 20	.736
Rockall (ER)	2.89 ± 1.2	2.51 ± 1.3	.002
ASA score	2.55 ± 0.68	2.27 ± 0.56	<.001
Laboratory values			
Hematocrit (%)	28.4 ± 8.7	28.7 ± 8.9	.710
Platelets ($\times 10^9$/L)	256 ± 133	243 ± 107	.247
INR	1.4 ± 1.19	1.2 ± 0.40	.013
BUN (mg/dL)	39 ± 33	34 ± 27	.05
Length of stay (mean, days)	11.4 ± 21.7	6 ± 8.5	<.001
Length of stay (median, days)	5.5 (1, 238)	3 (1, 62)	<.001
Rebleed within 30 days	25 (11%)	11 (5%)	.009
Mortality within 30 days	9 (4%)	8 (4%)	.718

ASA = American Society of Anesthesiologists; BUN = blood urea nitrogen; ICU = intensive care unit; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

Supplemental Table 2 Comparison of Gastric and Duodenal Ulcers

	Gastric Ulcer n = 245	Duodenal Ulcer n = 164	*P* Value
Helicobacter pylori			.014
Positive	116 (47%)	98 (60%)	
Negative	129 (53%)	66 (40%)	
NSAID	156 (64%)	90 (55%)	.080
Stigmata present	91 (37%)	74 (45%)	.107
Active bleeding	23 (25%)	26 (35%)	
Visible vessel	46 (51%)	37 (50%)	
Adherent clot	22 (24%)	11 (15%)	
Stigmata absent	154 (63%)	90 (55%)	
Pigmented spot	19 (12%)	9 (10%)	
Clean base	135 (88%)	81 (90%)	
Endoscopic therapy	91 (37%)	73 (45%)	.136
Epinephrine injection	11 (12%)	8 (11%)	
Thermal coagulation	4 (5%)	5 (7%)	
Hemoclip(s)	11 (12%)	5 (7%)	
Combination therapy	65 (71%)	55 (75%)	

NSAID = nonsteroidal anti-inflammatory drug.