Upper Gastrointestinal Hemorrhage: Have New Therapeutics Made a Difference?

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Abstract

Background—To explore the distribution of etiologies and risk factors of upper gastrointestinal hemorrhage (UGH) in the context of new pharmacologic therapies that may alter risk of UGH.

Methods—Retrospective study was performed on eligible UGH inpatients at two academic medical centers, between July 1, 2001-June 30, 2003. Administrative data and chart review were used to identify demographics, UGH risk factors and etiologies. Bivariate and multivariate analyses were performed to describe distributions and associations of risk factors and etiologies.

Results—UGH was identified in 227 subjects, with erosive disease (n=99, 44%), peptic ulcer disease (n=75, 33%) and variceal bleeds (n=39, 17%) accounting for the majority of bleeds. Known risk factors for UGH occurred in 70% (n=156) of subjects (prior UGH 43% (n=90), NSAID use 23% (n=52), ASA use 25% (n=57), NSAID + ASA use 6.6% (n=15)), while 19% (n=42) were using a proton-pump inhibitor and 5% (n=11) a cyclooxygenase-2 inhibitor. Subjects at site 1 were more likely to have erosive disease (OR 7.1, P<0.001) and less likely to have variceal bleeding (OR 0.12, P=0.009) in multivariate analyses. Preventive therapy did not differ between sites.

Conclusions—Unlike older studies, peptic ulcer disease was not the most common etiology, suggesting that advances in H pylori eradication may affect the epidemiology of UGH. Despite advances in therapeutics of acid-related disease, erosive disease accounted for the majority of UGH. Most subjects had risk factors for UGH and most were not receiving protective therapy. Large between site differences in the distribution of etiologies existed.

Keywords

Gastrointestinal hemorrhage; epidemiology

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Data were previously presented at the Society of Hospital Medicine 2005 Annual Meeting.
Introduction

Upper gastrointestinal hemorrhage (UGH) is a common cause of acute admission for hospitalization.\textsuperscript{1-3} However, recent advances in our understanding of erosive disease and peptic ulcer disease (PUD), two of the most common etiologies of UGH, have led to effective strategies to reduce the risk of UGH. Successful implementation of these strategies, such as treatment of \textit{Helicobacter pylori} and the use of proton pump inhibitors (PPIs) and selective cyclooxygenase-2 inhibitors (COX-2s) in place of traditional non-selective NSAIDs, may be able to significantly reduce rates of UGH caused by erosive disease and PUD.\textsuperscript{4-7}

Prior to these preventive treatments, PUD and erosive disease both acid related disorders, were the most common causes of UGH requiring admission to the hospital, accounting for 62\% and 14\% of all UGHs respectively.\textsuperscript{2} Given the widespread treatment of \textit{H. pylori} and use of PPIs and COX-2s, we might expect that the distribution of etiologies of UGH may have changed. However, there are limited data on the distribution of etiologies of UGH in the era of effective preventive therapy.\textsuperscript{8} If the distribution of etiologies causing patients to present with UGH has fundamentally changed with these new treatments, established strategies of managing acute UGH may need to be re-evaluated. Given that well established guidelines exist and that many hospitals use a protocol-driven management strategy to decide on the need for admission and/or intensive care unit (ICU) admission, changes in the distribution of etiologies since the widespread use of these new pharmacologic approaches may affect the appropriateness of these protocols.\textsuperscript{9,10} For example, if the eradication of \textit{H. pylori} has dramatically reduced the proportion of UGH caused by PUD then risk stratification studies developed when PUD was far more common may need to be re-visited. This would be particularly important if bleeding from PUD was of significantly different severity than bleeding from other causes.

While patients with \textit{H. pylori} related UGH from PUD should be treated for \textit{H. pylori} eradication, several important questions remain surrounding the use of newer therapeutics that may mitigate the risk of UGH in some patients. It is unclear what proportion of patients admitted with UGH in this new era developed bleeding despite using preventive therapy. These treatment failures are known to occur, but it is not well known how much of the burden of UGH today is due to this breakthrough bleeding.\textsuperscript{5,6,11,12} Contrastingly, there are also patients who are admitted with UGH who are not on preventive treatment. Current guidelines suggest that high-risk patients requiring NSAIDs be given COX-2s or traditional NSAIDs with a PPI.\textsuperscript{13-15} However, there is significant disagreement between these national guidelines about what constitutes a high-risk profile.\textsuperscript{13-15} For example, some guidelines recommend that elderly patients requiring NSAIDs should be on a PPI while others do not make that recommendation. Similarly, while prior UGH is a well recognized risk factor for future bleeding risk even without NSAIDs, current guidelines do not provide guidance towards the use of preventive therapy in these patients. If there are few patients who present with UGH related to acid disease that are not on a preventive therapy, then these unanswered questions or conflicts within current guidelines become less important. However, if a large portion of UGH is due to acid related disease in patients not on preventive therapy, then these unanswered questions may become important for future research.

In contrast to previous studies, the current study examines the distribution of etiologies of UGH in the era of widespread use of effective preventive therapy for erosive disease and PUD in two US academic medical centers. Prior studies were done before the advent of new therapeutics and did not compare different sites which may be important.\textsuperscript{16,17}
Methods

Patients

Consecutive patients admitted with UGH were identified at two academic medical centers as part of a larger observational study examining the impact of hospitalist physicians on the care of acute medical patients. The sample was selected from the 12,091 consecutive general medical patients admitted from July 2001-June 2003 with UGH identified by International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9 CM) codes from administrative data and confirmed by chart abstraction. ICD-9 CM codes for UGH included: esophageal varices with hemorrhage (456.0, 456.20), Mallory-Weiss syndrome (530.7), gastric ulcer with hemorrhage (531.00-531.61), duodenal ulcer with hemorrhage (532.00-532.61), peptic ulcer, site unspecified, with hemorrhage (533.00-533.61), gastrojejunular ulcer with hemorrhage (534.00-534.61), gastritis with hemorrhage (535.61), angiodysplasia of stomach/duodenum with hemorrhage (537.83), and hematemesis (578.0, 578.9). Finally, the admission diagnoses for all patients in the larger cohort were reviewed and any with gastrointestinal hemorrhage were screened for possible inclusion to account for any missed ICD-9 codes. Subjects were then included in this analysis if they had observed hematemesis, NG tube aspirate with gross or hemoccult blood, or history of hematemesis, bloody diarrhea, or melena upon chart review.

Data

The inpatient medical records were abstracted by trained researchers. Etiologies of UGH were assessed by esophagastroduodenoscopy (EGD) report which listed findings and etiologies as assessed by the endoscopist. Multiple etiologies were allowed if more than one source of bleeding was identified. Prior medical history and pre-admission medication use were obtained from three sources: 1. The emergency department medical record, 2. Nursing admission documentation, and 3. The admission history and physical documentation. Risk factors and pre-admission medication use were considered present if documented in any of the three sources. Relevant past medical history included known risk factors for UGH including: end-stage renal disease, alcohol abuse, prior history of UGH, and steroid use. Prior H. pylori status/testing could not reliably be obtained from these data sources. Pre-admission medication use of interest included aspirin, NSAIDS, anticoagulants, anti-platelet agents, as well as PPIs and COX-2s. Demographics including age, race, and gender were obtained from administrative databases.

We defined subjects as at-risk if they had any of the following risk-factors: prior UGH (at any time), use of an NSAID (traditional or selective COX-2), or use of an aspirin prior to admission. Patients taking COX-2s were included for two reasons. First, while COX-2 inhibitors are associated with a lower risk of UGH than traditional NSAIDs, it is likely that they still lead to an increased risk of UGH compared to placebo. Secondly, if a patient required NSAIDs of some type (traditional or selective), pre-admission use of a COX-2 rather than a traditional NSAID may reflect the intention of decreasing the risk of UGH compared to using traditional NSAIDs. In order to use the most conservative estimate of potential missed opportunities for prevention, pre-admission use of a PPI or COX-2 was considered preventive therapy. All pre-admission medication use was obtained from chart review. Therefore duration of and purpose for medication use were not available.

Development of the abstraction tool was performed by the authors. Testing of the tool was performed on a learning set of 20 charts at each center. All additional abstractors were trained with a learning set of at least 20 charts to assure uniform abstraction techniques.
Analysis

For each risk factor and etiology, we calculated the proportion of patients with the risk factor or etiology both overall and by site. Differences in risk factors between sites were assessed using chi-squared tests of association. Differences in etiologies between sites were assessed using unadjusted odds ratios as well as odds ratios from logistic regression models controlling for age, gender and race (black versus not black). Center 1 was the urban center and center 2 was the rural site.

This study was approved by the Institutional Review Board at the University of Iowa Carver College of Medicine and the University of Chicago.

Results

From the entire cohort of 12,091 admitted to the two inpatient medical services, 227 (1.9%) patients were identified as having UGH; 138 (61%) were from center 1 where 87% of patients were black and 89 (39%) were from center 2 where 89% of patients were white. Overall, the mean age was 59 years, 45% were female, and 41% were white. (Table 1)

The most common etiologies of UGH were erosive disease (44%), PUD (33%), and varices (17%) in the overall population. These same three etiologies were also the most common in both of the medical centers, although, there were significant differences in the rates of etiologies between the two centers. Erosive disease was more common among subjects from center 1 (59%) than from center 2 (19%) (P<0.001), while variceal bleeding was more common among subjects from center 2 (34%) than from center 1 (6.5%) (P=0.009). (Table 2)

In multivariate logistic regression analyses, only age and site remained independent predictors of etiologies. Advancing age was associated with a higher risk of arteriovenous malformations (AVMs) with the odds of AVMs increasing 6% for every additional year of life (P=0.007). Site was associated with both erosive disease and variceal bleeding. Patients from center 1 were significantly more likely to have UGH caused by erosive disease with an odds ratio of 7.10 (P<0.001) compared to subjects from center 2. However, subjects from center 1 had a significantly lower odds ratio (OR= 0.12) than those subjects at center 2 (P=0.009) of having UGH caused by a variceal bleed. (Table 2)

Risk factors for UGH were common among these patients, including use of aspirin (25.1%), NSAIDs (22.9%), COX-2s (4.9%), or prior history of UGH (43%). Additionally, 6.6% of patients were taking both an NSAID and aspirin. Differences between the two sites were seen only in aspirin use, with 34.8% of patients in the center 1 population using aspirin compared to 10.1% in center 2, (P<0.001). (Table 3)

Among the overall population, 68.7% of patients had identifiable risk factors (Prior history of UGH or pre-admission use of aspirin, NSAIDs, or COX-2s). 18.5% of all subjects were on PPIs and 4.9% were taking COX-2s while 21.1% of at risk subjects were on PPIs and 6.5% of these subjects were on a COX-2.

Finally, we examined the effects of variations in pre-admission medication use between the sites on the etiologies of UGH. None of the site-based differences in etiologies could be explained by differences in pre-admission medication patterns.

Discussion

Despite the emergence of effective therapies for lowering the risk of erosive disease and PUD, these remain the most common etiologies of UGH in our cohort of patients. In a
dramatic change from historically reported patterns, erosive disease was more common than PUD. In prior studies, PUD accounted for almost 2/3 of all UGH. While some of the newer therapeutics such as PPIs and COX-2s, reduce the risk for acid related bleeding of all types, *H. pylori* eradication is effective primarily for PUD. Therefore, it may be that widespread testing and treatment of *H. pylori* have dramatically decreased rates of PUD. Unfortunately, this study does not allow us to directly evaluate the effect of *H. pylori* treatment on the changing epidemiology of UGH as that would require a population based study.

While decreasing rates of PUD could explain a portion of the change in the distribution of etiologies, increasing rates of erosive disease could also be playing a role. Prior studies have suggested that African Americans and the elderly are more susceptible to erosive disease, particularly in the setting of NSAIDs and/or aspirin and less susceptible to cirrhosis. Our finding of a higher rate of erosive disease and lower rates of cirrhosis in center 1 with a higher proportion of African Americans and greater aspirin use is consistent with these prior findings. However, in multivariate analyses, neither race nor pre-admission medication use patterns explained the differences in etiologies seen. This suggests that some other factors must play a role in the differences between the two centers studied. These results emphasize the importance of local site characteristics in the interpretation and implementation of national guidelines and recommendations. This finding may be particularly important in diseases and clinical presentations that rely on protocol driven pathways, such as UGH. Current recommendations on implementing clinical pathways derived from national guidelines emphasize the fact that national development and local implementation optimization is probably the best approach for effective pathway utilization.

It is important to understand why erosive disease and PUD, for which we now have effective pharmacologic therapies, continue to account for such a large percentage of the burden of UGH. In this study, we found that a majority of subjects were known to have significant risk factors for UGH (aspirin use, NSAID use, COX-2s, or prior UGH) and only 31% of the subjects could not have been identified as at-risk prior to admission. PPIs or COX-2s should neither be used universally as preventive therapy nor are they completely effective at preventing UGH in at-risk patients. In this study, 2/3 of patients with risk factors were not on preventive therapy, but almost 1/3 of patients with risk factors had bleeding despite being on preventive therapy. A better understanding of why these treatment failures (bleeding despite preventive therapy) occur may be helpful in our future ability to prevent UGH. This study was not designed to determine if the 2/3 of patients not taking preventive therapy were being treated consistent with established guidelines. However, current guidelines have significant variation in recommendations about which patients are at high enough risk to warrant preventive therapy. and there is no consensus about which patients are at high enough risk to warrant preventive therapy. Our data suggest that additional studies will be required to determine the optimal recommendations for preventive therapy among at-risk patients.

There are several limitations to this study. First, it only included two academic institutions. However, these institutions represented very different patient populations. Secondly, the study design is not a population-based study. This limitation prevents us from addressing questions such as the effectiveness or cost-effectiveness of interventions to prevent admission for UGH. Although we analyzed pre-admission PPI or COX-2 use in at-risk patients as preventive therapy, we are unable to determine the actual intent of the physician in prescribing these drugs. Finally, although the mechanisms by which PPIs and COX-2 affect the risk of UGH are fundamentally different and should not be considered equivalent choices, we chose to analyze either option as representing a preventive strategy in order to provide the most conservative estimate possible of preventive therapy utilization rates.
However, our assumptions would generally overestimate the use of preventive therapy (as opposed to PPI use for symptom control) as we assumed all potentially preventive therapy was intended as such.

This study highlights several unanswered questions that may be important in the management of UGH. First, identifying factors that affect local patterns of UGH may better inform local implementation of nationally developed guidelines. Second, a more complete understanding of the impact positive and negative risk factors for UGH have on specific patient populations may allow for a more consistent targeted approach to using preventive therapy in at risk patients.

Finally, and perhaps most importantly, is to determine if the change in distribution of etiologies is in fact related to a decline in bleeding related to PUD. In addition to this being a marker of the success of the *H. pylori* story, it may have important implications on our understanding of the acute management of UGH. If PUD is of a different severity than other common causes of UGH, such as erosive disease, current risk stratification prediction models may need to be re-validated. For example, if UGH secondary to PUD results in greater morbidity and mortality than UGH secondary to ED, our current models identifying who requires ICU admission, urgent endoscopy, and other therapeutic interventions may result in over utilization of these resource intensive interventions. However if larger studies do not confirm this decline in PUD it suggests the need for additional studies to identify why PUD remains so prevalent despite the major advances in treatment and prevention of PUD through *H. pylori* identification and eradication.

**Acknowledgments**

This research was supported by TAP Pharmaceutical Products Inc., Lake Forest, IL. Dr. Kaboli is supported by a Research Career Development Award from the Health Services Research and Development Service, Department of Veterans Affairs (RCD 03-033). The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. The authors also wish to acknowledge support from Agency for Healthcare Research and Quality R01-HS10597, “A Multicenter Trial of Academic Hospitalists.”

**References**


Table 1
Baseline Characteristics of 227 Consecutive Upper Gastrointestinal Hemorrhage (UGH) Patients Admitted to 2 Academic Medical Centers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=227)</th>
<th>Center 1 (n=138)</th>
<th>Center 2 (n=89)</th>
<th>P-value Center 1 vs. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>58.6</td>
<td>59.5</td>
<td>57.1</td>
<td>0.317</td>
</tr>
<tr>
<td>% Female</td>
<td>44.5%</td>
<td>48.6%</td>
<td>38.2%</td>
<td>0.126</td>
</tr>
<tr>
<td>% White</td>
<td>41.2%</td>
<td>10.2%</td>
<td>88.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% African American</td>
<td>54.0%</td>
<td>86.9%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>% Other</td>
<td>4.9%</td>
<td>2.9%</td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2

Etiology of UGH and Differences by Study Site

<table>
<thead>
<tr>
<th>Etiology</th>
<th>ALL N=227</th>
<th>Center 1 N=138</th>
<th>Center 2 N=89</th>
<th>Unadjusted OR (95% CI): Center 1 vs.2</th>
<th>P value for Unadjusted OR</th>
<th>Adjusted a OR (95% CI): Center 1 vs.2</th>
<th>P value (for Adjusted OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosive Disease</td>
<td>43.6%</td>
<td>59.4%</td>
<td>19.1%</td>
<td>6.20 (3.31, 11.62)</td>
<td>&lt;0.001</td>
<td>7.10 (2.48, 20.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PUD</td>
<td>33.0%</td>
<td>37.0%</td>
<td>27.0%</td>
<td>1.59 (.89, 2.84)</td>
<td>0.119</td>
<td>1.33 (.48, 3.67)</td>
<td>0.578</td>
</tr>
<tr>
<td>Varices</td>
<td>17.2%</td>
<td>6.5%</td>
<td>33.7%</td>
<td>0.14 (.06, .31)</td>
<td>&lt;0.001</td>
<td>0.12 (.03, .60)</td>
<td>0.009</td>
</tr>
<tr>
<td>AVM</td>
<td>5.3%</td>
<td>2.9%</td>
<td>9.0%</td>
<td>0.30 (.09, 1.04)</td>
<td>0.057</td>
<td>0.21 (.03, 1.69)</td>
<td>0.141</td>
</tr>
<tr>
<td>Mallory Weiss Tear</td>
<td>4.9%</td>
<td>4.4%</td>
<td>5.6%</td>
<td>0.76 (0.23, 2.58)</td>
<td>0.664</td>
<td>0.34 (0.02, 4.85)</td>
<td>0.425</td>
</tr>
<tr>
<td>Cancer/Masses</td>
<td>2.6%</td>
<td>2.9%</td>
<td>2.3%</td>
<td>1.30 (0.23, 7.24)</td>
<td>0.766</td>
<td>0.62 (0.03, 12.12)</td>
<td>0.751</td>
</tr>
</tbody>
</table>

Numbers may add up to >100% as more than one etiology could be identified on endoscopy

*a Adjusted for age, gender, and black/not black. Mallory Weiss Tear not adjusted for gender since all were men

CI=Confidence Interval PUD= Peptic ulcer disease AVM= Arteriovenous malformation
### Table 3

Prevalence of Positive and Negative Risk Factors for UGH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All</th>
<th>Center 1</th>
<th>Center 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous UGH</td>
<td>42.7%</td>
<td>41.3%</td>
<td>45.2%</td>
<td>0.586</td>
</tr>
<tr>
<td>NSAID Use</td>
<td>22.9%</td>
<td>21.7%</td>
<td>24.7%</td>
<td>0.602</td>
</tr>
<tr>
<td>ASA Use</td>
<td>25.1%</td>
<td>34.8%</td>
<td>10.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID + ASA</td>
<td>6.6%</td>
<td>6.5%</td>
<td>6.7%</td>
<td>0.948</td>
</tr>
<tr>
<td>COX-2 Use</td>
<td>4.9%</td>
<td>6.5%</td>
<td>2.3%</td>
<td>0.143</td>
</tr>
<tr>
<td>PPI Use</td>
<td>18.5%</td>
<td>18.1%</td>
<td>19.1%</td>
<td>0.852</td>
</tr>
</tbody>
</table>

NSAID=non-steroidal anti-inflammatory drug, ASA=aspirin, COX=cyclooxygenase, PPI=proton-pump inhibitor