

Upper Gastrointestinal Hemorrhage: Have New Therapeutics Made a Difference?

Chad T. Whelan, MD¹
Peter Kaboli, MD, MS^{2,6}
Qi Zhang, PhD³
Juned Siddique, PhD⁴
Siqin Ye, MD⁵
David O. Meltzer, MD, PhD¹

¹ Department of Internal Medicine, University of Chicago, Chicago, Illinois.

² Center for Research in the Implementation of Innovative Strategies in Practice (CRIISP), Iowa City Veterans Administration (VA) Medical Center, Iowa City, Iowa.

³ School of Community and Environmental Health, Old Dominion University, Norfolk, Virginia.

⁴ Department of Preventive Medicine, Northwestern University, Evanston, Illinois.

⁵ Brigham and Women's Medical Center, Boston, Massachusetts.

⁶ Division of General Internal Medicine, Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa.

Supported by TAP Pharmaceutical Products, Inc., Lake Forest, IL; by a Research Career Development Award from the Health Services Research and Development Service, Department of Veterans Affairs (RCD 03-033 to P.K.); and by the Agency for Healthcare Research and Quality (R01-HS10597; "A Multicenter Trial of Academic Hospitalists"). The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. Data were previously presented at the Society of Hospital Medicine 2005 Annual Meeting.

Disclosure: Nothing to report.

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 the risk of UGH.

METHODS: Retrospective study performed on eligible UGH inpatients at 2 academic medical centers, between July 1, 2001 and June 30, 2003. Administrative data and chart review were used to identify demographics, UGH risk factors, and UGH 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 ED (n = 99; 44%), peptic ulcer disease (PUD) (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], nonsteroidal anti-inflammatory drug (NSAID) use 23% [n = 52], aspirin [ASA] use 25% [n = 57], NSAID + ASA use 6.6% [n = 15]), while 19% (n = 42) were using a proton-pump inhibitor (PPI) and 5% (n = 11) a cyclooxygenase-2 (COX-2) inhibitor. Subjects at site 1 were more likely to have ED (odds ratio [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, PUD was not the most common etiology, suggesting that advances in *Helicobacter pylori* (*H. pylori*) eradication may affect the epidemiology of UGH. Despite advances in therapeutics of acid-related disease, ED 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. *Journal of Hospital Medicine* 2009;4:E6–E10.

© 2009 Society of Hospital Medicine.

KEYWORDS: epidemiology, gastrointestinal hemorrhage.

Upper gastrointestinal hemorrhage (UGH) is a common cause of acute admission for hospitalization.^{1–3} However, recent advances in our understanding of erosive disease (ED) and peptic ulcer disease (PUD), 2 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 *Helicobacter pylori* (*H. pylori*) and the use of proton pump inhibitors (PPIs) and selective cyclooxygenase-2 inhibitors (COX-2s) in place of traditional nonselective nonsteroidal antiinflammatory drugs (NSAIDs), may be able to significantly reduce rates of UGH caused by ED and PUD.^{4–7}

Prior to these preventive treatments, PUD and ED, 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.² Given the widespread treatment of *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.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 reevaluated. 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.^{9,10} For example, if the eradication of *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 revisited. This would be particularly important if bleeding from PUD was of significantly different severity than bleeding from other causes.

While patients with *H. pylori*-related UGH from PUD should be treated for *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.^{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.^{13–15} However, there is significant disagreement between these national guidelines about what constitutes a high-risk profile.^{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 toward 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 ED and PUD in 2 U.S. academic medical centers. Prior studies were done before the advent of new therapeutics and did not compare different sites, which may be important.^{16,17}

PATIENTS AND METHODS

Patients

Consecutive patients admitted with UGH were identified at 2 academic medical centers as part of a larger observational study examining the impact of hospitalist physicians on the care of acute medical patients.¹⁸ The sample was selected from the 12,091 consecutive general medical patients admitted from July 2001 to 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 and 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), gastrojejunal ulcer with hemorrhage (534.00–534.61), gastritis with hemorrhage (535.61), angiodysplasia of stomach/duodenum with hemorrhage (537.83), and hematemesis (578.0 and 578.9).¹⁹ 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, nasogastric (NG) tube aspirate with gross or hemocult 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 esophago-gastroduodenoscopy (EGD) report, which listed findings and etiologies as assessed by the endoscopist. Multiple etiologies were allowed if more than 1 source of bleeding was identified. Prior medical history and preadmission medication use were obtained from 3 sources: (1) the emergency department medical record; (2) nursing admission documentation; and (3) the admission history and physical documentation. Risk factors and preadmission medication use were considered present if documented in any of the 3 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. Preadmission medication use of interest included aspirin, NSAIDs, anticoagulants, antiplatelet 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 2 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. Second, if a patient required NSAIDs of some type (traditional or selective), preadmission 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, preadmission use of a PPI or COX-2 was considered preventive therapy. All preadmission medication use was obtained from chart

TABLE 1. Baseline Characteristics of 227 Consecutive UGH Patients Admitted to 2 Academic Medical Centers

Characteristic	Total (n = 227)	Center 1 (n = 138)	Center 2 (n = 89)	P Value Center 1 versus 2
Mean age (years)	58.6	59.5	57.1	0.317
% Female	44.5	48.6	38.2	0.126
% White	41.2	10.2	88.8	<0.001
% African American	54.0	86.9	3.4	<0.001
% Other	4.9	2.9	7.9	<0.001

Abbreviation: UGH, upper gastrointestinal hemorrhage.

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-square tests of association. Differences in etiologies between sites were assessed using unadjusted odds ratios (ORs) as well as ORs 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 2 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 ED (44%), PUD (33%), and varices (17%) in the overall population. These same 3 etiologies were also the most common in both of the medical centers, although there were significant differences in the rates of etiologies between the 2 centers. ED 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 ED and variceal bleeding. Patients from center 1 were significantly more likely to have UGH caused by ED, with an OR = 7.10 ($P < 0.001$), compared to subjects from center 2. However, subjects from center 1 had a significantly lower OR (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 the 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 2 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 preadmission use of aspirin, NSAIDs, or COX-2s). Of all subjects, 18.5% 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 preadmission medication use between the sites on the etiologies of UGH. None of the site-based differences in etiologies could be explained by differences in preadmission medication patterns.

DISCUSSION

Despite the emergence of effective therapies for lowering the risk of ED and PUD, these remain the most common etiologies of UGH in our cohort of patients. In a dramatic change from historically reported patterns, ED was more common than PUD. In prior studies, PUD accounted for almost two-thirds of all UGH.² 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 ED could also be playing a role. Prior studies have suggested that African Americans and the elderly are more susceptible to ED, particularly in the setting of NSAIDs and/or aspirin use, and less susceptible to cirrhosis.^{13,16,17,20-23} Our finding of a higher rate of ED 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 preadmission medication use patterns explained the differences in etiologies seen. This suggests that some other factors must play a role in the differences between the 2 centers

TABLE 2. Etiology of UGH and Differences by Study Site

Etiology	All n = 227 (%)	Center 1 n = 138 (%)	Center 2 n = 89 (%)	Unadjusted OR (95% CI): Center 1 versus 2	P Value for Unadjusted OR	Adjusted* OR (95% CI): Center 1 versus 2	P Value (for Adjusted OR)
ED	43.6	59.4	19.1	6.20 (3.31–11.62)	<0.001	7.10 (2.48–20.31)	<0.001
PUD	33.0	37.0	27.0	1.59 (0.89–2.84)	0.119	1.33 (0.48–3.67)	0.578
Varices	17.2	6.5	33.7	0.14 (0.06–0.31)	<0.001	0.12 (0.03–0.60)	0.009
AVM	5.3	2.9	9.0	0.30 (0.09–1.04)	0.057	0.21 (0.03–1.69)	0.141
Mallory Weiss Tear	4.9	4.4	5.6	0.76 (0.23–2.58)	0.664	0.34 (0.02–4.85)	0.425
Cancer/masses	2.6	2.9	2.3	1.30 (0.23–7.24)	0.766	0.62 (0.03–12.12)	0.751

NOTE: Numbers may add up to >100% as more than 1 etiology could be identified on endoscopy.

Abbreviations: AVM, arteriovenous malformation; CI, confidence interval; PUD, peptic ulcer disease; UGH, upper gastrointestinal hemorrhage.

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

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.²⁴

It is important to understand why ED 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 not be used universally as preventive therapy, and they are not completely effective at preventing UGH in at-risk patients. In this study, two-thirds of patients with risk factors were not on preventive therapy, but almost one-third 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 two-thirds of patients not taking preventive therapy were being treated consistent with established guidelines. However, current guidelines have significant variation in recommendations as to which patients are at high enough risk to warrant preventive therapy,^{13–15} and there is no consensus as to 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 2 academic institutions. However, these institutions represented very different patient populations. Second, 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 preadmission 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

TABLE 3. Prevalence of Positive and Negative Risk Factors for UGH

Risk Factor	All (%)	Center 1 (%)	Center 2 (%)	P Value
Previous UGH	42.7	41.3	45.2	0.586
NSAID use	22.9	21.7	24.7	0.602
ASA use	25.1	34.8	10.1	<0.001
NSAID + ASA	6.6	6.5	6.7	0.948
COX-2 use	4.9	6.5	2.3	0.143
PPI use	18.5	18.1	19.1	0.852

Abbreviations: ASA, aspirin; COX, cyclooxygenase; NSAID, nonsteroidal antiinflammatory drug; PPI, proton-pump inhibitor.

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 ED, current risk stratification prediction models may need to be revalidated. 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 overutilization 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.

Address for correspondence and reprint requests:

Chad T. Whelan, MD, Section of General Internal Medicine, Department of Medicine, University of Chicago, 5841 South Maryland Avenue (MC2007), Chicago, IL 60637; Telephone: 773-834-5931; Fax: 773-834-2238; E-mail: cwhelan@uchicago.edu Received 6 February 2008; revision received 16 September 2008; accepted 21 September 2008.

REFERENCES

- Meltzer D, Manning WG, Morrison J, et al. Effects of physician experience on costs and outcomes on an academic general medicine service: results of a trial of hospitalists. *Ann Int Med.* 2002;137(11):866–874.
- Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol.* 1995;90(2):206–210.
- Czernichow P, Hochain P, Nousbaum JB, et al. Epidemiology and course of acute upper gastro-intestinal haemorrhage in four French geographical areas. *Eur J Gastroenterol Hepatol.* 2000;12:175–181.
- van der Hulst RW, Rauws EA, Koycu B, et al. Prevention of ulcer recurrence after eradication of *Helicobacter pylori*: a prospective long-term follow-up study. *Gastroenterology.* 1997;113:1082–1086.
- Lai KC, Hui WM, Wong WM, et al. Treatment of *Helicobacter pylori* in patients with duodenal ulcer hemorrhage—a long-term randomized, controlled study. *Am J Gastroenterol.* 2000;95:2225–2232.
- Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with *Helicobacter pylori* infection who are taking low-dose aspirin or naproxen. *N Engl J Med.* 2001;344:967–973.
- Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med.* 2002;346:2033–2038.
- van Leeram MD, Breeburn EM, Rauws EAJ, et al. Acute upper GI bleeding: did anything change?: time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol.* 2003;98:1494–1499.
- Hay JA, Lyubashevsky E, Elashoff J, et al. Upper gastrointestinal hemorrhage clinical guideline—determining the optimal length of stay. *Am J Med.* 1996;100:313–322.
- Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2003;139:843–857.
- Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med.* 2000;343:1520–1528.
- Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA.* 2000;284:1247–1255.
- AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc.* 2002;50(6 Suppl):S205–S224.
- Simon LS, Lipman AG, Jacox AK, et al. Pain in osteoarthritis, rheumatoid arthritis and juvenile chronic arthritis. 2nd ed. Clinical practice guideline no. 2. Glenview, IL: American Pain Society (APS);2002:179 p.
- American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum.* 2000;43:1905–1915.
- Rockall TA, Logan RFA, Devlin HB, et al. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *BMJ.* 1995;311:222–226.
- Kaplan RC, Heckbert SR, Koepsell TD, et al. Risk factors for hospitalized gastrointestinal bleeding among older persons. *J Am Geriatr Soc.* 2001;49:126–133.
- Meltzer D, Arora V, Zhang J, et al. Effects of inpatient experience on outcomes and costs in a multicenter trial of academic hospitalists. *Society of General Internal Medicine Annual Meeting* 2005.
- Cooper GS, Chak A, Way LE, Hammar PJ, Harper DL, Rosenthal GE. Early endoscopy in upper gastrointestinal hemorrhage: association with recurrent bleeding, surgery, and length of hospital stay. *Gastrointest Endosc.* 1999;49(2):145–152.
- Sterling RK, Stravitz RT, Luketic VA, et al. A comparison of the spectrum of chronic hepatitis C virus between Caucasians and African Americans. *Clin Gastroenterol Hepatol.* 2004;2:469–473.
- El-Serag HB, Peterson NJ, Carter C, et al. Gastroesophageal reflux among different racial groups in the United States. *Gastroenterology.* 2004;126:1692–1699.
- Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Risk factors for erosive reflux esophagitis: a case-control study. *Am J Gastroenterol.* 2001;96:41–46.
- Akhtar AJ, Shaheen M. Upper gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs in African-American and Hispanic elderly patients. *Ethn Dis.* 2003;13:528–533.
- Shojania K, Grimshaw J. Evidence-based quality improvement: the state of the science. *Health Aff (Millwood).* 2005;24(1):138–150.