

# **Upper Gastrointestinal Bleeding: An Evidence-Based Approach**

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## Evidence-based Medicine Is:

An approach to patient care in which critical appraisal of the most recent literature is used in conjunction with clinical experience and an understanding of basic pathophysiologic mechanisms

1973 marked the publication of the first edition of Sleisenger and Fordtran, arguably the preferred textbook of gastroenterology, certainly in Dallas. In that year, there was no proven benefit in the management of UGI bleeding for endoscopy, any medical therapy, or medical prevention. This discussion will trace the evidence that has accumulated over the ensuing 25 years in each of these areas, with an emphasis on non-variceal causes in general and peptic ulcer in particular. Validity criteria for randomized controlled trials and meta-analyses, the primary sources of evidence, will also be addressed.

## UGI Bleeding: 25 years of evidence

	<u>1973</u>	<u>1998</u>
Endoscopy	No Evidence of Benefit	Evidence of Benefit
Medical Therapy	No Evidence of Benefit	Evidence of Benefit
Medical Prevention	No Evidence of Benefit	Evidence of Benefit

## UGI Bleeding: 25 years of evidence

1973

- UGI series “preferred” test to diagnose peptic ulcers
- Treatment - Iced water lavage

In 1973, the recommended modality to diagnose peptic ulcers, the most common non-variceal cause of UGI hemorrhage, was the barium UGI series. The only treatment recommended for bleeding was iced-water lavage. Recommendations in 1978 shifted emphasis on diagnosis from x-ray to endoscopy, although evidence to show any benefit was not available.

## UGI Bleeding: 25 years of evidence

1978

- Endoscopy the “preferred” diagnostic test, although no evidence to support its benefit
- Treatment - lavage with Levophed
  - Bright red blood = cold lavage
  - Dark red blood = room temperature lavage

### Routine, Early Endoscopy: a randomized, controlled trial

- Patients with UGI bleeding that ceased were randomly assigned to early/no endoscopy
- All patients treated with antacid
- All patients had UGI series
- Surviving patients followed for up to 12 months

A randomized, controlled trial was conducted at the Dallas VAMC to determine if information gained at routine, early endoscopy provided any benefit to patients with UGI bleeding which ceased shortly after admission. Despite intense efforts by some individuals to halt the study because they believed it “unethical”, the study was completed (1).

### Routine, Early Endoscopy: a randomized, controlled trial

- No differences between the groups in recurrent bleeding, transfusions, mortality, or hospital stay
- No difference in 12 month follow-up

This results of this study were met with strong emotions. Those who distrusted the “new” technique of endoscopy, applauded it. Those who firmly believed making a diagnosis has inherent merit, criticized it. Why should a highly accurate diagnostic test not translate into some tangible benefit to patients with UGI bleeding? The answer is, simply, that in the late 70’s and early 80’s there was nothing of prognostic or therapeutic utility to which the information obtained at endoscopy could be directed.

## Reasons Why Endoscopy Was of No Benefit

- No prognostic value
- No therapeutic value
  - endoscopic
  - pharmacologic

## UGI Bleeding: 25 years of evidence

1981

- First prospective study demonstrating predictive value of different stigmata of hemorrhage in bleeding ulcers
- First studies of argon laser in bleeding ulcers
  - Stop active bleeding
  - ? Prevent rebleeding

The suggestion that the incidence of recurrent bleeding from ulcers differed depending on the appearance of the ulcer crater was a major observation that had an impact on all future studies of UGI bleeding (2). As more attention was paid to the appearance of the ulcer crater, early studies of endoscopic therapy were begun.

### Recurrent Bleeding from Ulcers (From Storey)

<u>Ulcer Feature</u>	<u>Further Bleeding</u>
Visible Vessel	19/34(56%)
Other SRH	1/13(8%)
No SRH	0/40(0%)

## UGI Bleeding: 25 years of evidence

1983

- Endoscopy recommended for patients with continuing bleeding - still no proven benefit
- Treatment:
  - ?Room temp lavage without Levophed
  - Endoscopic therapy - not proven
  - Pharmacologic therapy - not proven

The 1983 edition of Sleisenger and Fordtran's textbook retreated from some of the anecdotal recommendations of the past, and urged caution regarding others, but absent any data still relied on "expert opinion" in most of its suggestions. The following 15 years saw an explosion of data and finally evidence on which to base recommendations.

## UGI Bleeding: the last 15 years

- Information gained from endoscopy is beneficial
- Pharmacologic therapy beneficial
- Secondary prevention possible by non-surgical means

## UGI Bleeding: the last 15 years

- Information gained from endoscopy is beneficial
  - Endoscopic therapy improves outcome

The first area in which data were forthcoming was that benefit could accrue from endoscopic therapy of bleeding varices or ulcers. Much of the work in ulcer bleeding came from randomized trials of multipolar electrocoagulation conducted at Los Angeles County Hospital (3,4). The principal investigator in these trials later co-authored a sentinel meta-analysis of endoscopic therapy of bleeding ulcer (5).

### Endoscopic Therapy of Bleeding Ulcer (From Cook, et al)

<u>Appearance of Ulcer Crater</u>	<u>Further Bleeding</u>	<u>Mortality</u>
<u>Active/NBVV</u>		
No. of trials	19	16
OR (95%CI)	0.23 (0.15-0.27)	0.62 (0.38-0.98)
<u>Other SRH</u>		
No. of Trials	6	
OR (95% CI)	1.00(0.45-2.23)	N/A

## Critical Appraisal of a Meta-analysis

### What should you look for?

- Was there a focused clinical question?
- Were selection criteria appropriate?
- Were important articles missed?
- Was the validity of each article assessed?
- Were these assessments reproducible?
- Were results similar from study to study?

This meta-analysis met all the criteria for validity noted above and, indeed, endoscopic therapy of actively bleeding ulcers or those with non-bleeding visible vessels has become an evidence-based standard of care. We have also learned that prognostic information gained at endoscopy can lead to early refeeding, early discharge, and even safe outpatient management of patients with UGI bleeding.

## UGI Bleeding: the last 15 years

- Information gained from endoscopy is beneficial
  - Endoscopic therapy improves outcome
  - Hospital care can be tailored
    - refeeding
    - early discharge
    - outpatient management

## Immediate vs Delayed Refeeding in Patients with “benign” SRH (From Laine et al)

	Immediate Refeeding (n=127)	Delayed Refeeding (n=124)
Rebleeding	5(4%)	6(5%)
Mortality	1(1%)	1(1%)

One of the first studies utilizing prognostic information obtained at endoscopy showed that patients with Mallory-Weiss tears or peptic ulcers with a clean base could be safely re-fed immediately without adverse outcome (6). Other studies have now looked at various permutations of early discharge from hospital (7-11).

## Early Discharge of DU Patients at Low Risk of Rebleeding (From Lai et al)

- 75 patients less than 60 y/o with stable vital signs and no SRH were discharged on the same day as endoscopy
- There were no instances of recurrent hematemesis or melena and no significant drop in hemoglobin after one week

## Prospective Evaluation of a Clinical Guideline for LOS After UGI Bleeding (From Hay et al)

- An evidence-based risk stratification scoring system for recurrent bleeding was devised and retrospectively validated
- Independent predictors included hemodynamics, co-morbidities, and endoscopic findings
- Discharge of low-risk patients was predicted to save 2.1 bed days/pt

The group at Cedars Sinai in Los Angeles performed two superb studies in which a clinical pathway for UGI bleeding was designed and validated and then tested in a controlled clinical trial (9,10). For the first time, it was convincingly shown that information gained at endoscopy could lead to a significantly better outcome in terms of hospital stay, cost of hospitalization, and patient satisfaction without compromising patient safety (11).

## Prospective Evaluation of a Clinical Guideline for LOS After UGI Bleeding (From Hay et al)

- The safety, acceptability, and impact of this length-of-stay guideline was prospectively tested
- Study was prospective, controlled time-series with alternate month design
- Most important predictor of a shorter length of hospital stay was early endoscopy

## Effect of Clinical Practice Guideline on Hospital Stay (From Hay et al)

	Implementation <u>Months</u>	Control <u>Months</u>
Adherence to Guideline	70%	30%
Length of Stay (Days)	2.9	4.6
ICU Stay (Days)	1.3	1.8

Further data are now emerging that patients can be triaged in the Emergency Room and selected for immediate discharge and follow-up as outpatients (12).

## Outpatient Management of Acute UGI Hemorrhage (From Longstreth)

- A practice guideline was developed to identify patients for outpatient care; the main criterion was absence of high-risk endoscopic features
- 176 patients were given outpatient care
- Only 2 patients were subsequently admitted to the hospital

## UGI Bleeding: the last 15 years

- Information gained from endoscopy is beneficial
- Pharmacologic therapy beneficial
  - Prevention of early ulcer rebleeding with acid suppression

It was hoped that, based on their good results in non-bleeding ulcers, that H<sub>2</sub> receptor antagonists would decrease the incidence of in-hospital ulcer rebleeding. A landmark meta-analysis summarized the results of 27 randomized trials of cimetidine or ranitidine in 1673 patients with bleeding duodenal or gastric ulcer (13). The authors concluded that these drugs appeared to be promising, at least in gastric ulcer, and called for large-scale studies to confirm their benefit.

## Recurrent Bleeding with H<sub>2</sub> Blocker or Placebo: A Meta-analysis

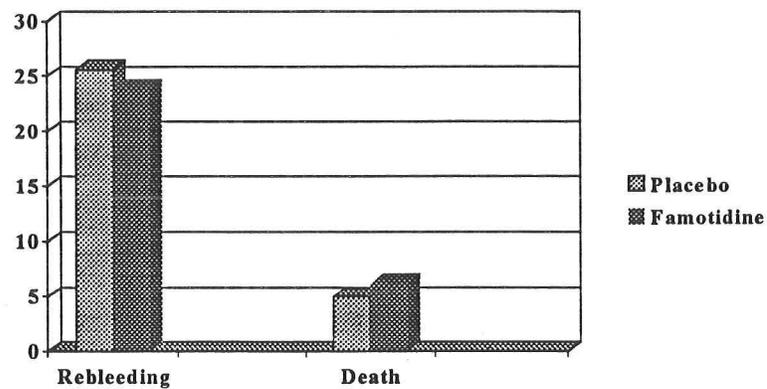
	<u>H<sub>2</sub> Blocker</u>	<u>Placebo</u>
DU	25%	25%
GU	27%	21%

## Continuous Intravenous Famotidine for Peptic Ulcer Bleeding (Walt, Lancet 1992)

- 1005 patients whose bleeding ulcer had either oozing, fresh clot, NBVV, or “black slough”
- IV famotidine (3.2mg/h) or placebo for 72h
- Study was double blind

Such a study was performed, but rebleeding rates and mortality were very similar in patients treated either with intravenous famotidine or placebo (14).

## Rebleeding and Death from Peptic Ulcer (Walt)



## Critical Appraisal of Article on Therapy What should you look for?

- Pre-Study:
  - Concealed randomization
  - Groups comparable to start
- During Study:
  - Equal co-interventions
  - Blinding
- Post-Study:
  - All patients accounted for
  - ITT analysis

## Possible Reasons Why H<sub>2</sub> Blockers Do Not Decrease Ulcer Rebleeding

- Gastric acidity has nothing to do with recurrent ulcer bleeding
- H<sub>2</sub> Blockers do not lower acidity adequately to have a pharmacologic effect

In an attempt to settle the issue of adequate reduction of acidity, our group at the Dallas VAMC devised a regimen which achieved consistent pH levels of 7.0 in duodenal ulcer patients (15). A randomized, controlled trial was instituted to test the hypothesis that sustained achlorhydria would decrease the incidence of recurrent ulcer bleeding.

## Reduction of Acidity to Prevent Recurrent Ulcer Bleeding -the Dallas saga-

- Regimens were studied to find one to sustain pH at or above 7.0
- A combination regimen of cimetidine 100mg/h IV infusion + antacid 0.5ml/min NG infusion was selected for a randomized, blinded controlled trial
- Standard cimetidine bolus used as control

## Rebleeding with Double Infusion or Control

<u>Ulcer Base</u>	<u>Control</u>	<u>Double Inf.</u>	<u>Total</u>
Clean	1/13	0/12	1/25 (4%)
Spot	0/9	2/10	2/19 (10%)
Clot	2/11	3/10	5/21 (24%)
NBVV	<u>1/2</u>	<u>1/3</u>	2/5 (40%)
	4/35 (11%)	6/35 (17%)	

After three years and 70 patients randomized, the code was broken. The double infusion regimen conferred no benefit. Unfortunately, there were too few patients with lesions at high enough risk for rebleeding (e.g., clot, NBVV) to hope to show a benefit for any regimen. The study was halted. The role of acid suppression has resurfaced with recent reports from India and Taiwan that show omeprazole may be effective when used alone or in combination with endoscopic therapy (16,17). The following represents a review of RCT's evaluating the effect of a proton pump inhibitor on recurrent bleeding in hospitalized patients with endoscopically- documented bleeding peptic ulcers (16-23).

## Proton Pump Inhibitors in Acute Peptic Ulcer Bleeding

- Eight RCT's were identified in which omeprazole was compared with placebo or an H<sub>2</sub> blocker in patients with bleeding ulcer
- Three were excluded from review
  - Grosso: Groups not comparable
  - Hasselgren: Data not interpretable
  - Schaffalitzky: Data not interpretable

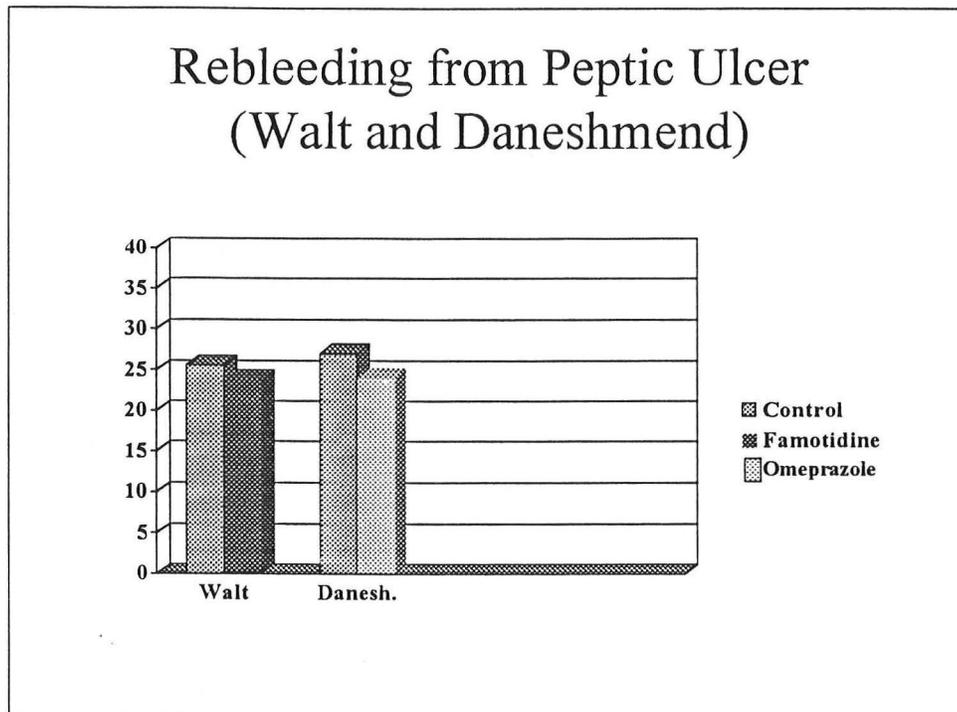
## Proton Pump Inhibitors in Acute Peptic Ulcer Bleeding

- Three studies were in patients receiving no endoscopic therapy
- Two studies were in patients whose ulcer was treated with injection or thermal therapy

The first study was carried out by the same UK group that performed the large study using intravenous famotidine (18). Note that omeprazole is not available for intravenous use in North America.

## Omeprazole vs Placebo for Acute UGI Hemorrhage (Daneshmend)

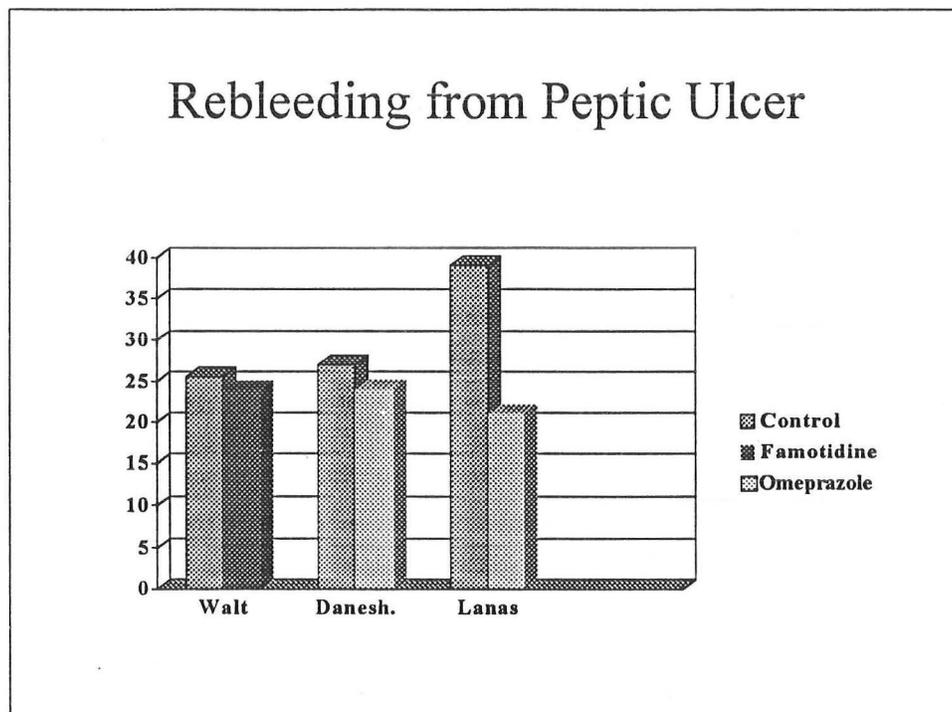
- 1147 “all comers” with UGI hemorrhage were randomly assigned to IV omeprazole or placebo
- Endoscopy was performed in 92% within 24hours
- 3% of ulcer bleeders received endoscopic therapy
- Study was double blind



Their results were remarkably similar to those obtained using famotidine, suggesting that, in UK patients with a broad range of stigmata of hemorrhage, acid suppression is of no benefit in patients with bleeding ulcer. Another study from Spain came to different conclusions (19).

### Omeprazole vs Ranitidine in Bleeding Peptic Ulcer (Lanas)

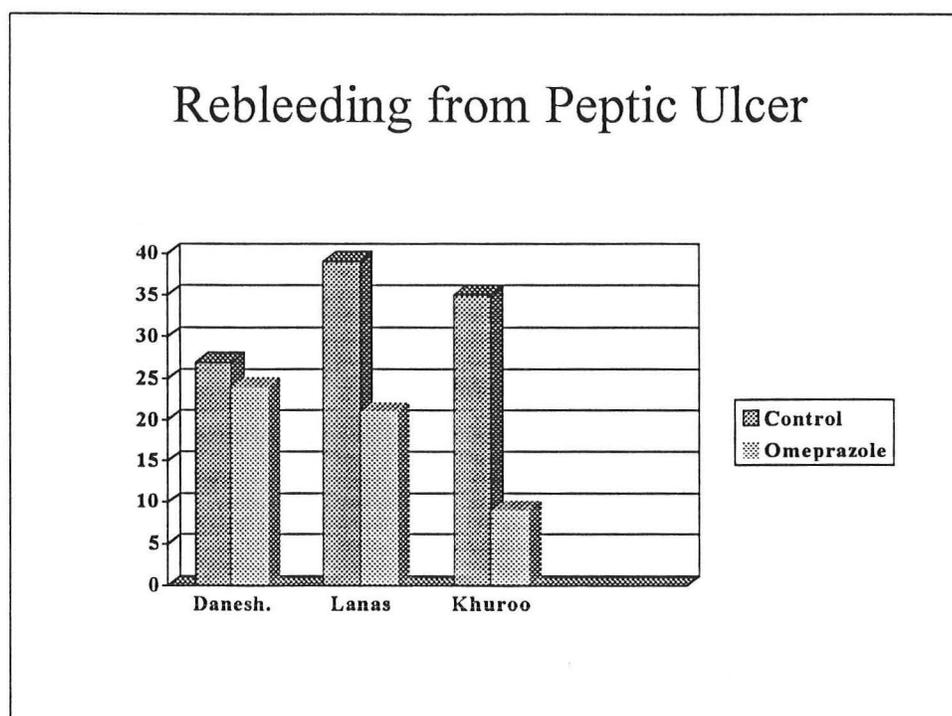
- 51 patients with peptic ulcer with oozing, NBVV, or adherent clot were randomly assigned to IV omeprazole or ranitidine
- No endoscopic therapy was given
- Study was not blinded



The rebleeding rates of 39% with ranitidine and 21% with omeprazole were not significantly different, most likely because of the small sample sizes. Ulcers with clots made up the majority of lesions and in them, rebleeding occurred in 33% with ranitidine and 20% with omeprazole. This study was unblinded, a major drawback. Much more striking results were obtained by Khuroo and colleagues (16).

### Omeprazole vs Placebo for Bleeding Peptic Ulcer (Khuroo)

- 220 patients with peptic ulcer with spurting, oozing, NBVV, or clot were randomly assigned to oral omeprazole or placebo
- No endoscopic therapy was provided
- Bleeding continued in only 5 patients
- Study was double blind



This was an impeccably designed, blinded study that included patients with active bleeding, NBVV, and clots. Omeprazole was given orally in a dose of 40mg q12h and no endoscopic therapy was available. Overall rebleeding rates of 35% and 9% were significantly different. As shown below, rebleeding was decreased in each lesion, but the most striking results were with NBVV and clots.

### Ulcer Rebleeding with Omeprazole or Control

	<u>Spurting</u>	<u>Oozing</u>	<u>NBVV</u>	<u>Clot</u>
<b>Lanas</b>				
Cont		2/4	2/4	5/15
Omeprazole		1/5	1/3	4/20
<b>Khuroo</b>				
Cont	11/12	3/16	10/18	13/61
Omeprazole	6/9	2/18	2/17	0/64

## Omeprazole in Bleeding Ulcer Without Endoscopic Therapy

### -Summary-

- The Khuroo study shows oral omeprazole to be highly effective in preventing rebleeding from ulcers which present with a NBVV or a clot
- The Lanas study using IV omeprazole is not as strong, but supports the conclusion re:clots
- Data not compelling for ulcers actively bleeding at initial endoscopy

The data from the Khuroo study are compelling for ulcers not bleeding at the initial endoscopy. Why they showed benefit and the UK group (18) did not is a matter of speculation. The mix of stigmata may have been different and/or the effect on acid secretion may have been greater. Regardless, patients in the U.S. who have active bleeding or a NBVV are routinely treated with either injection or thermal therapy. What are the results with omeprazole after endoscopic therapy?

## Omeprazole vs Ranitidine After Injection Therapy of Actively Bleeding Ulcers (Villanueva)

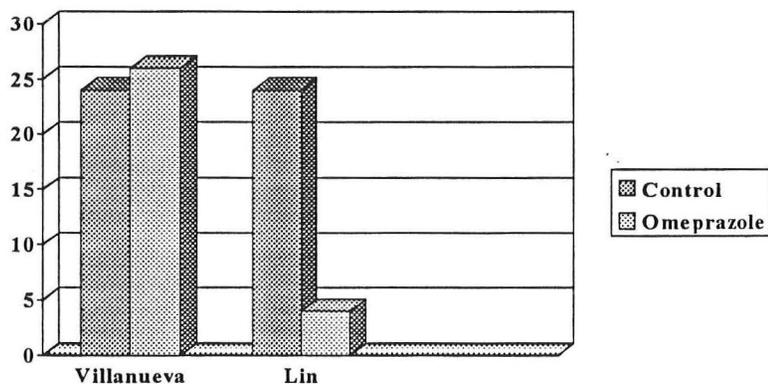
- 86 patients with spurting (10%) or oozing (90%) ulcers treated with epinephrine injection were randomly assigned to IV omeprazole or ranitidine co-therapy
- Bleeding continued in 5 patients
- The study was non-blinded
- Rebleeding occurred in 9/38 (24%) control patients and 11/43 (26%) with omeprazole

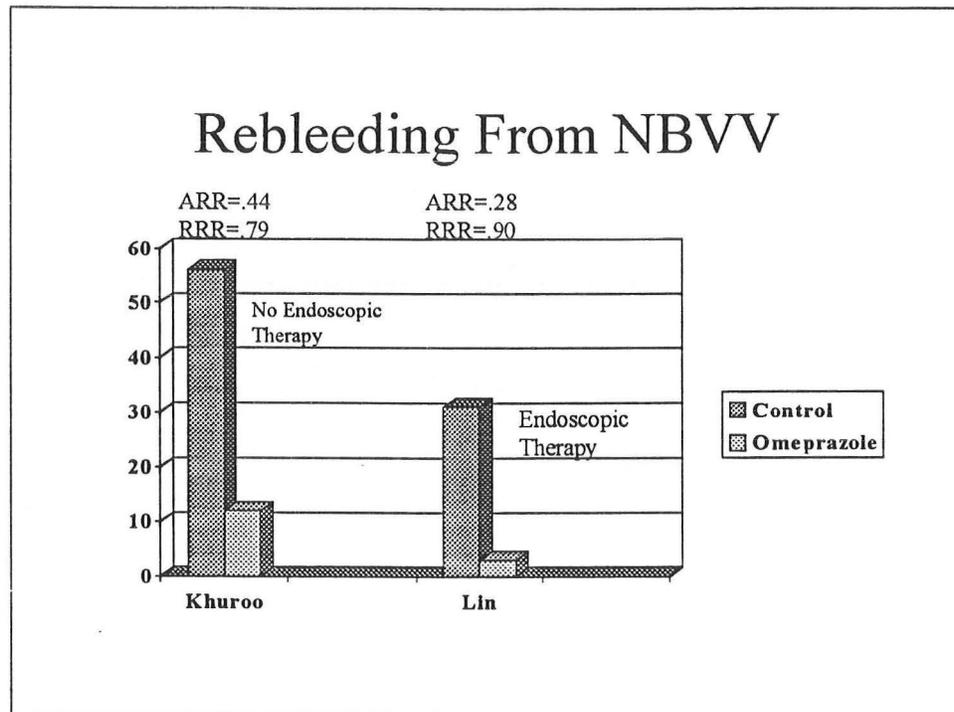
## Omeprazole vs Cimetidine After Thermal Therapy of Bleeding Ulcer (Lin)

- 100 patients with ulcers with spurting, oozing, or NBVV successfully treated with thermal therapy were randomly assigned to IV omeprazole or cimetidine
- The study was not blinded

In each of these non-blinded studies, the ulcers were treated endoscopically before randomization to omeprazole or control (17,20). While the overall rebleeding rate with control was very similar in the two studies, the results with omeprazole were much better in the Lin study. This may well be because the Valenzuela study enrolled only patients whose ulcer was actively bleeding while Lin also enrolled patients whose ulcers had NBVV.

## Ulcer Rebleeding After Endoscopic Therapy with Omeprazole or Control





When the results for NBVV in the Khuroo (no endoscopic therapy) and Lin (endoscopic therapy) studies are compared, one finds the control rebleeding rate in the latter to be much lower than in Khuroo's study and the absolute risk reduction (ARR) with omeprazole less. This reflects the benefit of endoscopic therapy. However, the degree of benefit with omeprazole (RRR=relative risk reduction) is quite comparable in the two studies.

## Omeprazole in Bleeding Ulcer After Endoscopic Therapy

- Patients who present with actively bleeding ulcers which are successfully treated with endoscopic therapy do not appear to benefit from concurrent omeprazole therapy
- Concurrent therapy with omeprazole after thermal therapy of an ulcer with a NBVV results in a decreased rebleeding rate

## UGI Bleeding: the last 15 years

- Information gained from endoscopy is beneficial
- Pharmacologic therapy beneficial
- Secondary prevention possible by non-surgical means
  - Acid suppression
  - Eradication of *H. pylori*

For many years, physicians treated patients who had bled from an ulcer with long-term maintenance H<sub>2</sub>-receptor antagonists in the belief that this would reduce the incidence of recurrent ulcer bleeding. Validation of this approach was achieved with the publication by Jensen and colleagues of a randomized, controlled trial of ranitidine vs. placebo (24).

## Prevention of Recurrent DU Bleeding with Ranitidine

(From Jensen)

- 65 patients with bleeding DU were randomly assigned to long-term treatment with ranitidine 150mg hs or placebo
- Follow-up was up to 3 years, with a mean of 61 weeks
- Rebleeding occurred in 36% of the control group and 9% of the ranitidine group

## Prevention of Recurrent Ulcer Bleeding by Eradication of Hp

- Five studies published
- Two studies randomized (Rokkas; Jaspersen)
- Patients treated with Om alone or Om + Antibiotics followed by no maintenance

With the recognition of *Helicobacter pylori* as a major risk factor for peptic ulcers and that eradication of the infection dramatically decreased the incidence of ulcer recurrence, it was proposed that rebleeding could also be decreased with eradication. Five studies have been published dealing with this issue (25-29), two of which were randomized (28,29). Based on the results of the two randomized studies, 3-4 patients would need to be treated (NNT) with eradication therapy to prevent recurrent bleeding in one patient.

## Prevention of Recurrent Ulcer Bleeding by Eradication of Hp

- Rebleed after Om alone = 33% (Rokkas) and 27% (Jaspersen)
- Rebleed after Om + Antibiotics = 0%
- ARR = 0.33 (95%CI .09-.57); 0.27 (.09-.46)
- NNT= 3-4 patients

## Comparison of Long-Term Acid Suppression and Eradication of *H. pylori* (From Riemann)

- 95 consecutive patients with ulcer bleeding randomized
  - ranitidine 150 mg hs
  - eradication of *H. pylori*
- Mean follow-up 576 days

A randomized trial has compared eradication of *H. pylori* with long-term acid suppression and shown that eradication therapy was significantly better in preventing recurrent ulcer and at least as effective in preventing recurrent bleeding (30). Unfortunately, the study was unblinded.

## Comparison of Long-Term Acid Suppression and Eradication of *H.*

	<u>Ranitidine</u>	<u><i>H. pylori</i> Eradication</u>
Recurrent Ulcer	15/48 (31.3%)	3/47 (6.3%)
Recurrent Bleeding	4/48 (8.3)	2/47 (4.2%)

## Summary

A substantial body of evidence (much of it high quality) has accumulated over the past 25 years to guide us in the management of patients with UGI bleeding. While not the focus of this Grand Rounds, modalities for the primary prevention of esophago-gastric variceal bleeding, the treatment of acutely bleeding varices, and prevention of rebleeding are now firmly evidence based. There is good evidence to justify the routine use of urgent endoscopy for prognostic and therapeutic purposes, reasonable evidence for the use of proton pump inhibitors to treat patients whose peptic ulcers are at risk for rebleeding, and modest early data for eradication of *H. pylori* as a means of long-term prevention of recurrent ulcer bleeding.

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