Upper Gastrointestinal Bleeding Peptic Ulcer Disease

Pharmacotherapy Issues in Acute Management and Secondary Prevention

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Objectives

- To discuss the acute management of upper GI bleeding peptic ulcers with a focus on antisecretory therapy.
- To discuss secondary prevention strategies following acute stabilization of acute GI bleeding peptic ulcers.

Epidemiology

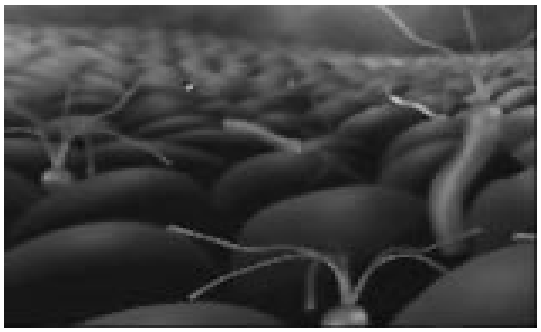
- ~15,000 admissions annually in Canada
- 55% caused by peptic ulcer disease
  - Helicobacter pylori
  - ASA/NSAIDS/COX-2 Inhibitors
- 80% will stop spontaneously
- 6-7% mortality rate
  - 0.6% if <60 years of age and no co-morbidity
  - 15% if >60 years of age and/or co-morbidity

Economic Implications

Marshall et al. (Am J Gastroenterol 1999;94:1841-6)

Age (yrs)	Total Cost	LOS (days)
18-39	**$1830**	**2.96**
40-59	**$2435**	**3.82**
60-74	**$2713**	**4.73**
75-85	**$5364**	**7.62**
Mean (n=116)	**$2690**	**4.26**

Helicobacter pylori



NSAID-Induced Peptic Ulcer Disease

- 15-30% of all PUD is NSAID-induced
- NSAID use increases risk of PUD 3-5X
- 60% of NSAID users experience heartburn, pain, dyspepsia
- symptoms >4 weeks have increased risk of gastric ulceration
- 66% of all NSAID users will have endoscopic evidence of gastric lesions but clinical ulcers is 2-4% annually

Risk Factors for NSAID-Induced Gastropathy

Wolfe et al. (NEJM 1999;320:1888-98)

Definite:

- Age
- Prior history of ulcer
- Duration of NSAID therapy
- Concomitant corticosteroid therapy
- Concomitant warfarin therapy
- Concomitant ASA/NSAID
- NSAID dose
- Serious systemic illness (CHF, RA, CAD, others)

Possible:

- Concomitant *H. pylori* infection?
- Smoking
- Alcohol

Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study

Francisco José de Abajo, Luis Alberto García Rodríguez, Dolores Montero

	No (%) of cases (n=1651)	No (%) of controls (n=10 000)	Adjusted relative risk* (95% CI)
Non-use	1115 (67.5)	8180 (81.8)	1
Current use			
Non-steroidal anti-inflammatory drugs	295 (17.9)	652 (6.5)	3.7 (3.2 to 4.4)
Selective serotonin reuptake inhibitors	38 (2.3)	93 (0.9)	2.6 (1.7 to 3.8)
Non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors	16 (1.0)	9 (0.1)	15.6 (6.6 to 36.6)

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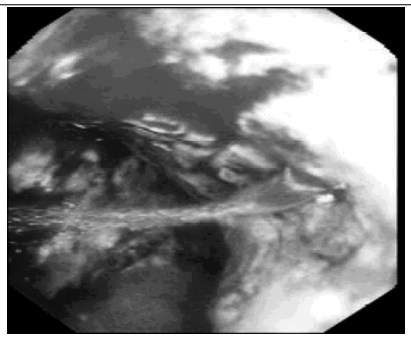
Acute Gastrointestinal Bleeding Peptic Ulcer



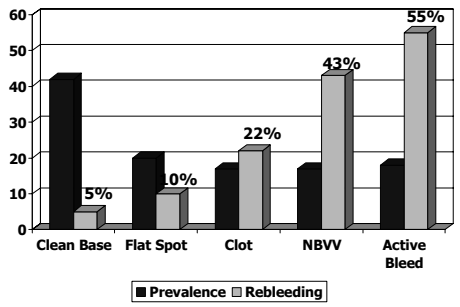
Prognostic Factors: Clinical

Barkun et al. (Aliment Pharmacol Ther 1999;13:1565-84)

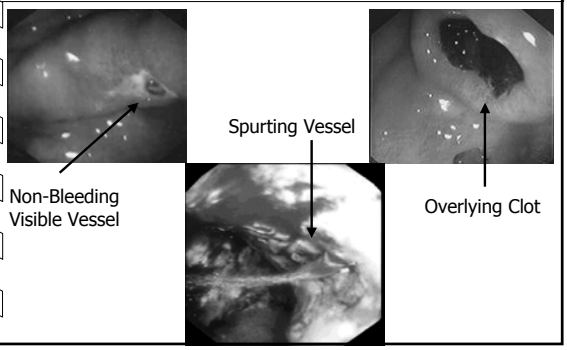
- hemodynamic instability
- hematochezia from upper GI source
- >60 years of age
- units of transfused blood
- concurrent illness
- onset of bleeding while hospitalized
- coagulopathy

Prognostic Factors: Endoscopic

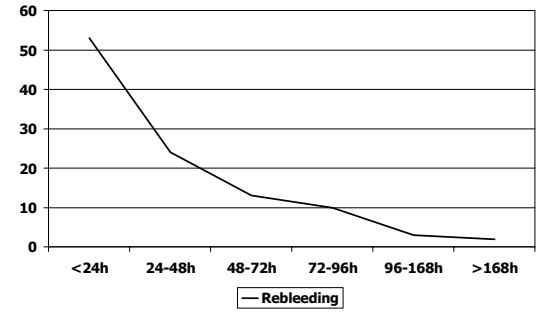
Barkun et al. (Aliment Pharmacol Ther 1999;13:1565-84)



High Risk Bleeds



Time to Rebleeding



Goals of Therapy

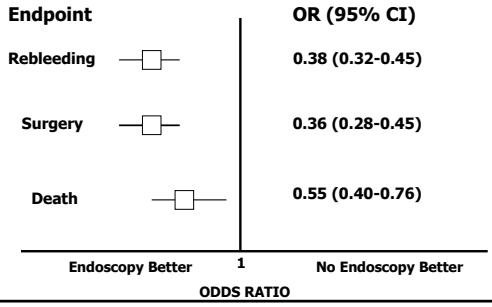
- Hemodynamic Stabilization and Resuscitation (ABC)
- Determine Cause
- Stop Bleeding
- Prevent Recurrence

Management

- Oxygen
- Fluid
- Blood Transfusion
- Endoscopic Therapy
- Surgery
- Pharmacotherapy

Endoscopic Therapy: Meta-Analysis

Cook et al. Gastroenterol 1992;102:139-48



Pharmacological Therapy

- Splanchnic blood pressure modifiers
  - vasopressin, octreotide, somatostatin
- Antifibrinolytic Agents
  - tranexamic acid
- **Antisecretory Agents**
  - **H2-receptor antagonists (H2RA)**
  - **proton-pump inhibitors (PPI)**

Role of Gastric Acid on Hemostasis

- Impairs clot formation
  - impairs platelet aggregation and causes disaggregation
- Accelerates clot lysis
  - acid-stimulated pepsin
- Impairs mucous/bicarbonate barrier

Aliment Pharmacol Ther 1999;106:1565-84

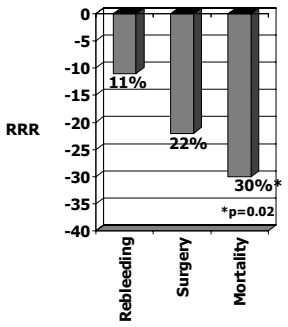
H2RA in Acute GI Bleeding: Meta-Analysis

Collins et al. (NEJM 1985;313:660-6)

- 27 trials, N=2500
- randomized, placebo-controlled trials
- H2RA vs. Placebo

ENDPOINTS

- rebleeding
- surgery
- mortality



Famotidine in Acute GI Bleeding

Walt et al. (Lancet 1992;340:1058-62)

Acute Endoscopically-proven GI Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=1005

Famotidine 10 mg IV bolus followed by 3.2 mg/h x 72h

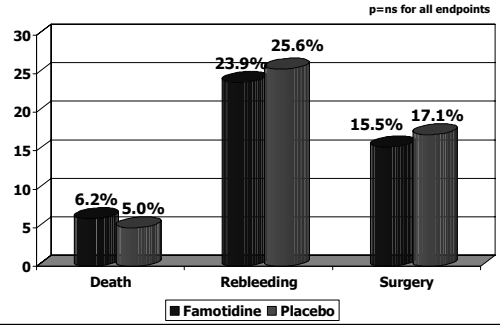
Placebo

ENDPOINTS:
Primary: Death during hospitalization

Secondary: Rebleeding
Surgery

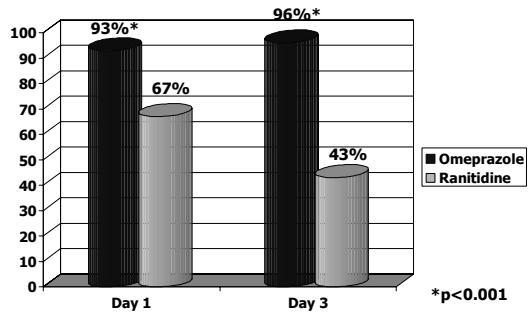
Famotidine in Acute GI Bleeding

Walt et al. (Lancet 1992;340:1058-62)



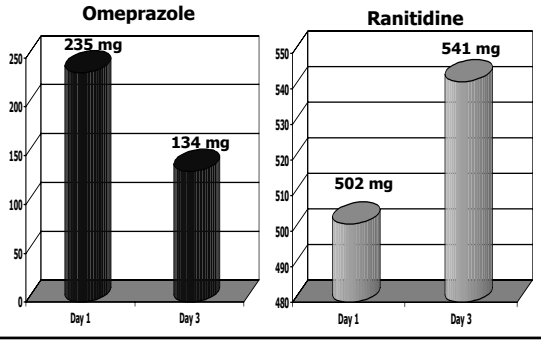
Tolerance: Intragastric pH>4

Merki and Wilder-Smith (Gastroenterol 1994;106:60-4)



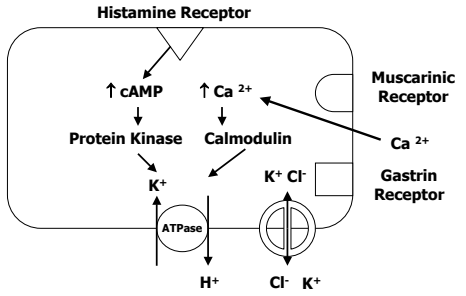
Tolerance: Daily Dose

Merki and Wilder-Smith (Gastroenterol 1994;106:60-4)



Proton-Pump Inhibitors

Mechanism of Action



PPI is Acute GI Bleeding Peptic Ulcers

- 12 randomized, controlled trials since 1990
- omeprazole only PPI evaluated in these trials
- 5 placebo-controlled, 7 H2RA-controlled

Issues

- Efficacy? Safety? Cost?
- PPI Alone vs. Adjuvant to Endoscopy?
- PPI Alone vs. Endoscopy Alone?
- Intermittent Dosing vs. Continuous Infusion?
- IV vs. PO?

Omeprazole: Intermittent Bolus

Daneshmend et al. (BMJ 1992;304:143-7)

Clinically-Diagnosed Acute GI Bleeding
P, MC, R, DB, PC
n=1147

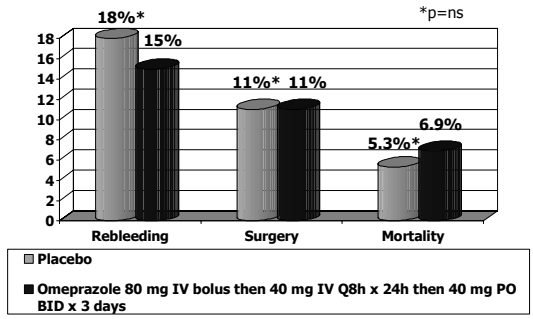
Omeprazole 80 mg IV bolus followed by 40 mg IV Q8h x 24h followed by 40 mg PO BID x 3 days

Placebo

ENDPOINTS:
Primary: **Death**
Rebleeding
Surgery
Transfusion

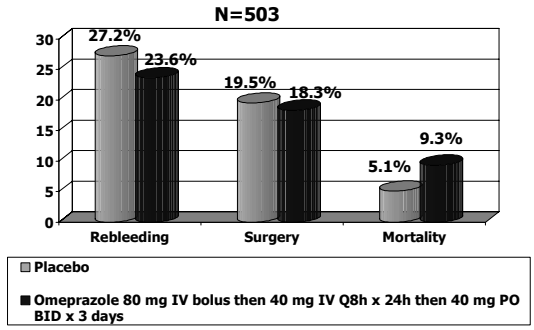
Omeprazole: Intermittent Bolus

Daneshmend et al. (BMJ 1992;304:143-7)



Proven Gastric/Duodenal Ulcer

Daneshmend et al. (BMJ 1992;304:143-7)



Omeprazole: Intermittent Bolus/Endoscopy

Villanueva et al. (Endoscopy 1995;27:308-12)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, R, OL
n=86

Omeprazole 80 mg IV bolus followed by 40 mg IV Q8h x 4 days followed by 20 mg PO daily

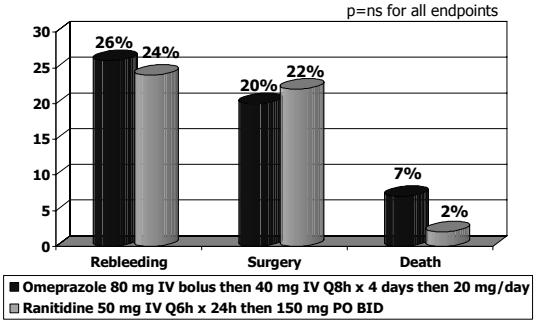
Ranitidine 50 mg IV Q6h x 24h followed by 150 mg PO BID

All patients received endoscopic therapy within 4h

ENDPOINTS:
Primary: **Death**
Rebleeding
Surgery

Omeprazole: Intermittent Bolus/Endoscopy

Villanueva et al. (Endoscopy 1995;27:308-12)



Summary: Intermittent Bolus

Study	PPI	Control	Result
Brunner (1990)	Omeprazole (n=19)	Ranitidine (n=20)	↓ **Bleeding**
Daneshmend (1992)	Omeprazole (n=578)	Placebo (n=569)	No Difference
Lanas (1995)	Omeprazole (n=23)	Ranitidine (n=23)	↓ **Surgery**
Villanueva (1995)	Omeprazole (n=45)	Ranitidine (n=41)	No Difference
Grosso (1995)	Omeprazole (n=21)	Endo/Ran (n=21)	No Difference
TOTAL	**Omeprazole N=686**	**Control N=674**	

Omeprazole: Continuous Infusion/Endoscopy

Schaffalitzky et al. (Scand J Gastroenterol 1997;32:320-7)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=265

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days

Placebo

All patients received endoscopic therapy within 12h

ENDPOINTS: Overall Outcome (ordinal scale)
Primary Variables:
Death (5)
Surgery (4)
Endoscopic Treatment (3)
Transfusion > 3 units (2)
Transfusion 1-3 units (1)

Omeprazole: Continuous Infusion/Endoscopy

Schaffalitzky et al. (Scand J Gastroenterol 1997;32:320-7)

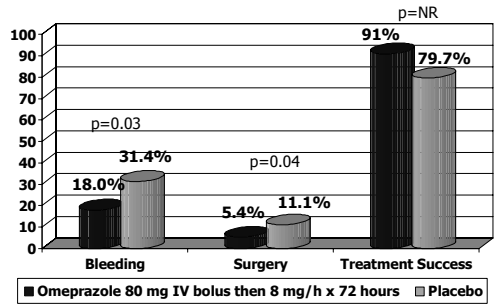
Overall Outcome of Treatment after 72 hours

Category	Outcome	Omeprazole* (n=130)	Placebo (n=135)

***p=0.0004**

Omeprazole: Continuous Infusion/Endoscopy

Schaffalitzky et al. (Scand J Gastroenterol 1997;32:320-7)



Omeprazole: Continuous Infusion

Hasselgren et al. (Scand J Gastroenterol 1997;32:328-33)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=322

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days

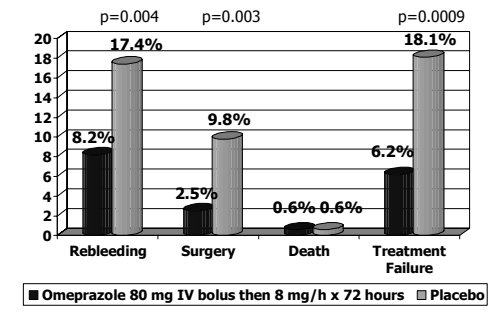
Placebo

ENDPOINTS:
Overall Outcome (ordinal scale)
Primary Variables:
Death (5)
Surgery (4)
Endoscopic Treatment (3)
Transfusion > 3 units (2)
Transfusion 0-3 units (1)

Secondary Variables:
Degree of bleeding
Duration of bleeding
Surgery
Endoscopic Treatment
Mortality
Treatment Failure

Omeprazole: Continuous Infusion

Hasselgren et al. (Scand J Gastroenterol 1997;32:328-33)



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EFFECT OF INTRAVENOUS OMEPRAZOLE ON RECURRENT BLEEDING AFTER ENDOSCOPIC TREATMENT OF BLEEDING PEPTIC ULCERS

JAMES Y.W. LAU, M.B., B.S., JOSEPH J.Y. SUNG, M.D., KENNETH K.C. LEE, PH.D., MAN-YEE YUNG, B.N., SIMON K.H. WONG, M.B., CH.B., JUSTIN C.Y. WU, M.B., CH.B., FRANCIS K.L. CHAN, M.D., ENDERS K.W. NG, M.B., CH.B., JOYCE H.S. YOU, PHARM.D., C.W. LEE, M.PHIL., ANGUS C.W. CHAN, M.B., CH.B., AND S.C. SYDNEY CHUNG, M.D.

Omeprazole: Continuous Infusion/Endoscopy

Lau et al. (NEJM 2000;343:310-6)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, R, DB, PC
n=240

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days followed by 20 mg PO daily x 8 wks

Placebo x 3 days followed by omeprazole 20 mg PO daily x 8 wks

All patients received endoscopic therapy within 24h

ENDPOINTS:
Primary: **Rebleeding at 30 days**

Secondary: **Surgery at 30 days**
Death at 30 days

TABLE 2. OUTCOMES AFTER ENDOSCOPIC THERAPY.

OUTCOME	OMEPRAZOLE GROUP (N=120)	PLACEBO GROUP (N=120)	RELATIVE RISK (95% CI)*	P VALUE
Recurrent bleeding — no. of patients				
By day 3	5	24	4.80 (1.89–12.2)	<0.001
By day 7	7	26	3.71 (1.68–8.23)	<0.001
By day 30	8†	27†	3.38 (1.60–7.13)	<0.001
Recurrent bleeding within 30 days — no. of patients/total no.				
Actively bleeding ulcers	3/64	10/58	4.24 (1.10–16.3)	0.04
Ulcers with nonbleeding visible vessels	5/56	17/62	3.85 (1.31–11.3)	0.02
Endoscopic retreatment successful — no. of patients	6	24	3.83 (1.62–9.08)	<0.001
Surgery — no. of patients	5	9	3.00 (0.83–10.8)	0.14
Median hospital stay <5 days — no. of patients (%)	58 (48.7)	38 (31.7)		0.02
Duration of hospitalization — days				
Patients admitted for bleeding peptic ulcers				
Median	4	5		0.006
Range	3–65	3–64		
Patients in whom bleeding developed in the hospital				
Median	13	9		0.33
Range	3–40	4–46		
Units of blood transfused‡	2.7±2.5	3.5±2.8		0.04
Before endoscopic therapy	1.0±1.3	1.1±1.5		0.46
After endoscopic therapy	1.7±1.9	2.4±2.2		0.03
Death within 30 days — no. of patients	5	12	2.40 (0.87–6.60)	0.13
Ulcer healing at 8 wk — no. of patients/total no. assessed endoscopically	72/85	77/83	1.10 (0.98–1.22)	0.14

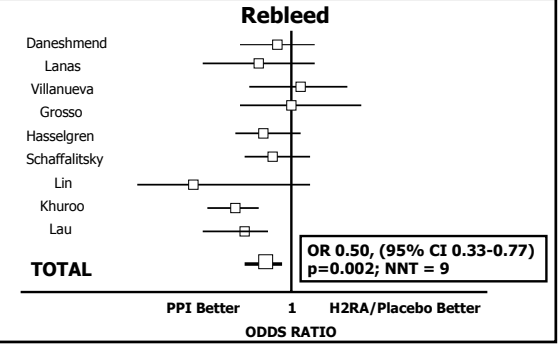
*Values indicate the relative risk of an outcome in the placebo group as compared with the omeprazole group. CI denotes confidence interval.
†This number is the total number of patients in the group who had recurrent bleeding within 30 days after treatment.
‡Plus–minus values are means ±SD.

Summary: Continuous Infusion

Study	PPI	Control	Result
Hasselgren (1997)	Omeprazole (n=159)	Placebo (n=163)	↑ **Overall Outcome** ↓ **Rebleeding** ↓ **Surgery**
Schaffalitzky (1997)	Omeprazole (n=130)	Placebo (n=135)	↑ **Overall Outcome** ↓ **Rebleeding** ↓ **Surgery**
Lin (1998)	Omeprazole (n=50)	Ranitidine (n=50)	↓ **Rebleeding**
Lau (2000)	Omeprazole (n=120)	Placebo (n=120)	↓ **Rebleeding**
TOTAL	**Omeprazole N=459**	**Control N=468**	

Meta-Analysis

Zed PJ et al. (Ann Pharmacother 2001;35:1528-34)



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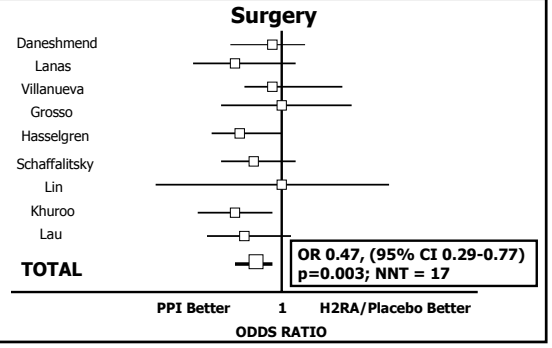


Omeprazole vs. Omeprazole/Endoscopy

Sung et al. (Ann Intern Med 2003;139:237-43)

Acute Endoscopically-proven High Risk Peptic Ulcer
NBVV/Adherent Clot
P, R, SB, PC
n=156

Endoscopy | **Sham Endoscopy**

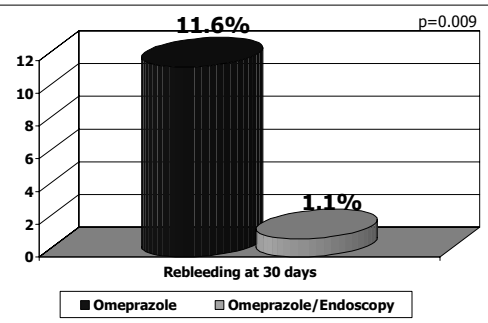
All patients omeprazole 80 IV bolus then 8 mg/h x 72h

ENDPOINTS:
Primary: **Rebleeding at 30 days**

Secondary: **Surgery at 30 days**
Death at 30 days

Omeprazole vs. Omeprazole/Endoscopy

Sung et al. (Ann Intern Med 2003;139:237-43)



Omeprazole: Oral Dosing

Khuroo et al. (NEJM 1997;336:1054-8)

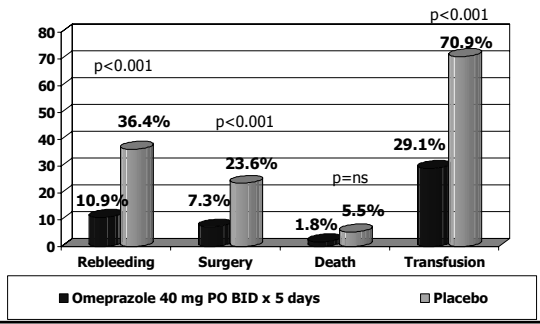
Acute Endoscopically-proven GI Bleeding Peptic Ulcer
P, R, DB, PC
n=220

Omeprazole
40 mg PO BID x 5 days | **Placebo**

ENDPOINTS:
Primary: **Death**
Rebleeding
Surgery
Transfusion

Omeprazole: Oral Dosing

Khuroo et al. (N Engl J Med 1997;336:1054-8)



Omeprazole: Oral Dosing

Javid et al. (Am J Med 2001;111:280-4.)

Acute Endoscopically-proven GI Bleeding Peptic Ulcer
P, R, DB, PC
n=166

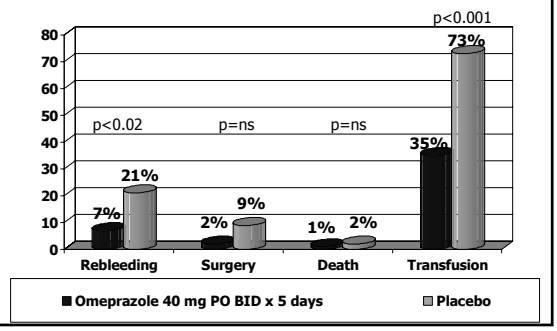
Omeprazole
40 mg PO BID x 5 days | **Placebo**

All patients received endoscopic therapy within 24h

ENDPOINTS:
Primary: **Rebleeding**
Surgery
Transfusion

Omeprazole: Oral Dosing

Javid et al. (Am J Med 2001;111:280-4.)



Consensus Recommendations for Managing Patients with Nonvariceal Upper Gastrointestinal Bleeding

Alan Barkun, MD, MSc; Marc Bardou, MD, PhD; and John K. Marshall, MD, MSc, for the Nonvariceal Upper GI Bleeding Consensus Conference Group*

Ann Intern Med. 2003;139:843-857.

Background: The management of patients with acute nonvariceal upper gastrointestinal bleeding has evolved substantially over the past 10 years amid a paucity of published consensus guidelines.

Purpose: To provide evidence-based management recommendations that address clinically relevant issues.

Review and Consensus Processes: A multidisciplinary consensus group of 25 voting participants representing 11 national societies used a 7-step approach to develop recommendation statements according to accepted standards. Sources of data included narrative and systematic reviews as well as published and new meta-analyses. The quality of the evidence, the strength of the recommendation, and the level of consensus were graded according to recognized classifications.

Main Findings: Recommendations emphasize appropriate initial resuscitation of the patient and a multidisciplinary approach to clinical risk stratification that determines the need for early endoscopy. Early endoscopy allows safe and prompt discharge of selected patients classified as low risk. Endoscopic hemostasis is reserved for patients with high-risk endoscopic lesions. Although monotherapy with injection or thermal coagulation is effective, the combination is superior to either treatment alone. The placement of endoscopic clips for endoscopic hemostasis appears promising. High-dose intravenous proton-pump inhibition is recommended in patients who have undergone successful endoscopic therapy. Routine second-look endoscopy is not recommended. Patients with upper gastrointestinal bleeding should be tested for *Helicobacter pylori* infection and receive eradication therapy if infection is present.

Future Directions: The efficacy of newer endoscopic therapeutic technologies, the optimal regimen of proton-pump inhibition, and the roles of other pharmacologic agents require further research.

Ann Intern Med. 2003;139:843-857. www.annals.org

For author affiliations, see end of text.

* For a list of the voting participants in the Nonvariceal Upper GI Bleeding Consensus Conference Group, see the Appendix, available at www.annals.org.

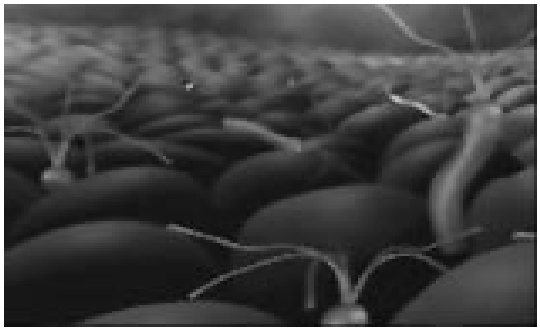
Conclusions

- H2RA have no role in the management of AGIB
  - cannot provide necessary pH increase
  - tolerance develops quickly
  - no benefit in clinical trials
- PPI beneficial in select patient populations
  - maintains desired intragastric pH
  - tolerance has not been reported

Conclusions

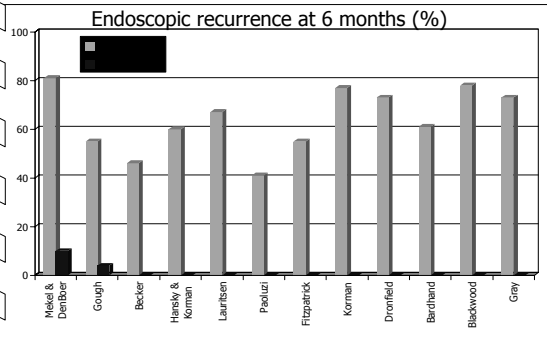
- Intermittent Dosing of PPI minimal benefit
- Continuous Infusion PPI offers most promising results
  - endoscopically-proven "high-risk" bleeding peptic ulcer
  - reduced rebleeding and need for surgery
  - no reduction in mortality
  - pantoprazole 80 mg IV bolus followed by 8 mg/h x 72 hours
- Future Research
  - IV vs. PO?
  - Role of pre-endoscopy PPI

Helicobacter pylori



H.pylori & Duodenal Ulcer Recurrence

O'Brien et al. (Arch Intern Med 1995;155:1958-64)



Prevention of Recurrence:

H.pylori Eradication

		Rebleeding	
Study	**Cure Rate**	**Control**	**H. pylori Tx**
Graham (1993)	**76%**	**29%**	**0%**
Labenz (1994)	**100%**	**38%**	**0%**
Rokkas (1995)	**81%**	**33%**	**0%**
Jaspersen (1995)	**83%**	**27%**	**0%**
Santander (1995)	**79%**	**12%**	**2%**
Maier (1995)	**90%**	**12%**	**0%**

H.pylori Eradication

Can J Gastroenterol 1998;12:31-41

FIRST LINE	SECOND LINE
PPI PO BID* Metronidazole 500 mg PO BID Clarithromycin 250 mg PO BID **PPI-MC 250**	PPI PO BID* Bismuth ii tabs PO QID Metronidazole 250 mg PO QID Tetracycline 500 mg PO QID **PPI-BMT**
PPI PO BID* Metronidazole 500 mg PO BID Clarithromycin 500 mg PO BID **PPI-MC 500**	Ranitidine 300 mg PO BID Bismuth 120 mg PO QID Metronidazole 250 mg PO QID Tetracycline 500 mg PO QID **R-BMT** **(14 day regimen)**
PPI PO BID* Amoxicillin 1000 mg PO BID Clarithromycin 500 mg PO BID **PPI-AC**	

*Omeprazole 20 mg or Lansoprazole 30 mg or Pantoprazole 40 mg

Prevention: Misoprostol (MUCOSA)

Silverstein et al. (Ann Intern Med 1995;123:241-9)

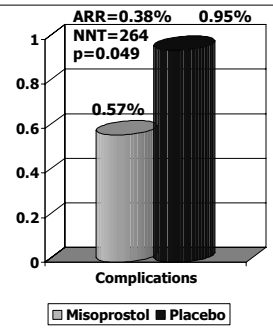
- P, MC, R, DB, PC N=8843
- RA, >52 yrs, NSAID-users

Misoprostol 200 mcg PO QID

vs.

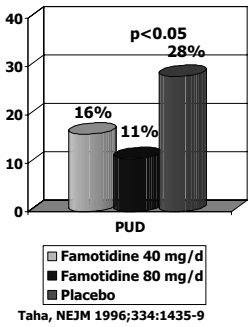
Placebo

ENDPOINT
Serious GI Complications
at 6 months

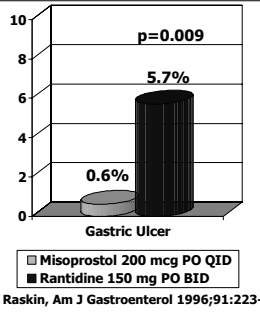


Prevention: H2RA

NSAID-Induced Peptic Ulcer Disease



Taha, NEJM 1996;334:1435-9



Raskin, Am J Gastroenterol 1996;91:223-7

Treatment and Prevention of Recurrence

NSAID-Induced Peptic Ulcer Disease

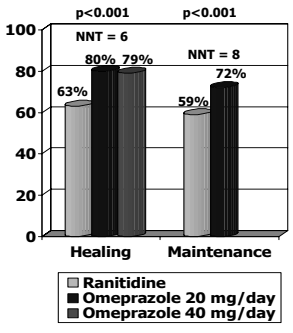
ASTRONAUT

(N Engl J Med 1998;338:719-26)

- P, MC, R, DB, N=541
- NSAID-induced PUD
- Ranitidine vs. Omeprazole

ENDPOINTS

- Healing at 8 weeks
- Maintenance at 6 months



Treatment and Prevention of Recurrence

NSAID-Induced Peptic Ulcer Disease

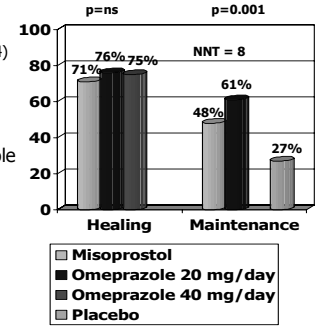
OMNIUM

(N Engl J Med 1998;338:727-34)

- P, MC, R, DB, N=935
- NSAID-induced PUD
- Misoprostol vs. Omeprazole

ENDPOINTS

- Healing at 8 weeks
- Maintenance at 6 months



The New England Journal of Medicine

(N Engl J Med 2002;347:2104-10.)

CELECOXIB VERSUS DICLOFENAC AND OMEPRAZOLE IN REDUCING THE RISK OF RECURRENT ULCER BLEEDING IN PATIENTS WITH ARTHRITIS

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ABSTRACT

Background Current guidelines recommend that patients at risk for ulcer disease who require treatment for arthritis receive nonsteroidal antiinflammatory drugs (NSAIDs) that are selective for cyclooxygenase-2 or the combination of a nonselective NSAID with a proton-pump inhibitor. We assessed whether celecoxib would be similar to diclofenac plus omeprazole in reducing the risk of recurrent ulcer bleeding in patients at high risk for bleeding.

Methods We studied patients who used NSAIDs for arthritis and who presented with ulcer bleeding. After their ulcers had healed, we randomly assigned patients who were negative for *Helicobacter pylori* to receive either 200 mg of celecoxib twice daily plus daily placebo or 75 mg of diclofenac twice daily plus 20 mg of omeprazole daily for six months. The end point was recurrent ulcer bleeding.

NONSTEROIDAL antiinflammatory drugs (NSAIDs) are one of the most widely prescribed classes of drugs worldwide, with nearly $2 billion spent in the United States yearly on prescription NSAIDs alone.[1] Gastrointestinal toxic effects induced by NSAIDs are common. In the United States, an estimated 107,000 patients are hospitalized and 16,500 die each year as a result of NSAID-related ulcer complications.[2] Patients with a history of ulcer bleeding who use NSAIDs are at the highest risk for ulcer complications.[3,4]

Current evidence indicates that concurrent therapy with NSAIDs and proton-pump inhibitors or misoprostol reduces the risk of ulcers[5,6] and ulcer complications.[7-9] Because proton-pump inhibitors are well tolerated, their use as prophylaxis has been recommended for patients at high risk for ulcer complications.[10,11]

Celecoxib vs. Diclofenac/Omeprazole

Chan et al. (NEJM 2002;347:2104-10)

OA/RA, H. pylori-negative
endoscopically-proven healed peptic ulcer
P, R, DB, PC
n=287

Celecoxib 200 mg PO BID
Placebo po daily
x 6 months

Diclofenac 75 mg PO BID
Omeprazole 20 mg PO daily
x 6 months

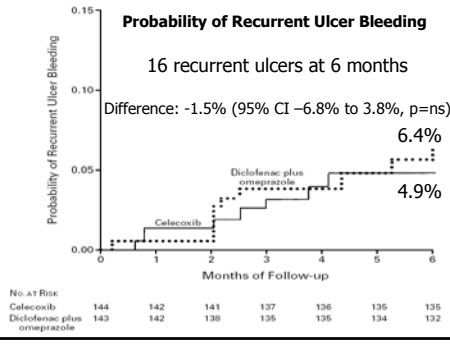
All patients received endoscopic evaluation every 2 months x 3

PRIMARY ENDPOINT: Rebleeding within 6 months

- clinical features/Hg drop + endoscopic confirmation

Celecoxib vs. Diclofenac/Omeprazole

Chan et al. (NEJM 2002;347:2104-10)



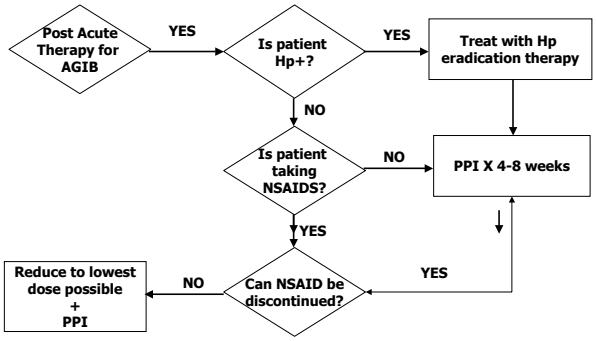
Celecoxib vs. Diclofenac/Omeprazole

Chan et al. (NEJM 2002;347:2104-10)

Table 4. Incidence of Adverse Events.

Event	Celecoxib (N=144)	Diclofenac plus Omeprazole (N=143)
	no. of patients (%)	
Gastrointestinal		
Dyspepsia	22 (15.3)	12 (8.4)
Nausea, heartburn, or diarrhea	1 (0.7)	2 (1.4)
Total	23 (16.0)	14 (9.8)
Discontinued medication	6 (4.2)	5 (3.5)
Renal		
Hypertension	20 (13.9)	27 (18.9)
Peripheral edema	7 (4.9)	8 (5.6)
Renal failure*	8 (5.6)	9 (6.3)
Total	35 (24.3)	44 (30.8)
Discontinued medication	7 (4.9)	7 (4.9)
Cardiovascular		
Myocardial infarction	1 (0.7)	0
Angina	1 (0.7)	2 (1.4)
Total	2 (1.4)	2 (1.4)
Discontinued medication	2 (1.4)	2 (1.4)

*Renal failure was defined by a progressive rise in the creatinine level to above 2.2 mg per deciliter (200 μmol per liter). There were no significant differences between the groups.



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