


## Gastroduodenal Ulcers: Still a Clinically Relevant Problem

David C. Metz, MD  
Division of Gastroenterology, Hospital of the University of Pennsylvania  
University of Pennsylvania School of Medicine  
Philadelphia, PA




## Disclosures

**Grant/Research Support** – AAA, Lexicon, Wren Labs, Ispen Biopharmaceuticals, Inc, Ironwood Pharmaceuticals

**Consultant** – GSK, Takeda, Novartis


**Member, Scientific Advisory Board** – Healing NET Foundation

**Member, Board of Directors** – North American Neuroendocrine Tumor Society



## Objectives

1. To review the pathophysiology of PUD
  - Imbalance of aggressive and defensive factors
2. To discuss each major cause of PUD
  - Hypersecretion
  - *H. pylori* infection
  - NSAIDs
3. To review the complications of PUD
  - Bleeding




## Peptic Ulcer Trends in the USA

Uncomplicated ulcers are declining:

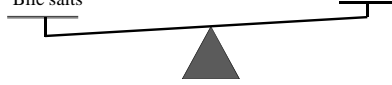
- Frequent use of PPIs and H2RAs
- Disappearance/Rx of *H. pylori* infection
- Judicious use of NSAIDs and ASA, introduction of Coxibs
- Better management of ICU patients (less stress related mucosal disease) (SRMD))


Bleeding ulcer prevalence is unchanged resulting in an increasing proportion overall



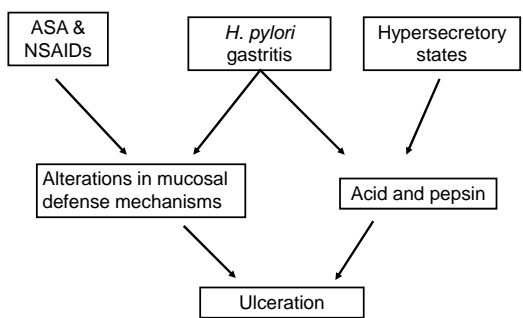
## Peptic Ulcer: An Imbalance Between

Aggressive Factors	Defensive Factors
Acid Pepsin Bile salts	Mucus/mucosal barrier Bicarbonate Blood flow Cell regeneration Prostaglandins





## Peptic Ulcer Disease Pathogenesis



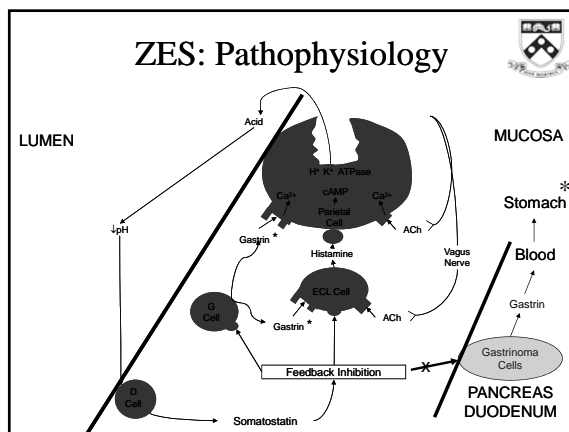
## i. Gastric Acid Hypersecretion

## Zollinger Ellison Syndrome \*

- Non-beta islet cell tumor (secretes gastrin)
- Gastric acid hypersecretion
- Fulminant peptic ulcer disease

\* Zollinger and Ellison, 1955

## ZES: Pathophysiology



## ZES: Inappropriate Hypergastrinemia is the Hallmark

- Gastric acid hypersecretion (Gastric analysis)
  - isolated measurement of limited value
- Elevated gastrin level
  - isolated level of limited value
- Inappropriate hypergastrinemia is the hallmark
  - Elevated acid output AND serum gastrin

## Consider ZES (<1/1000 DU's)

- Severe peptic disease:
  - Multiple, recurrent, non-healing ulcers
- Acid hypersecretion:
  - Diarrhea
- Before anti-ulcer surgery:
  - Before it's too late
- MEN-1 syndrome:
  - Pituitary, parathyroids, pancreas (3p's)
- Non-NSAID, non-*H. pylori* ulcers

## ii. NSAID Gastropathy

### NSAID Gastropathy

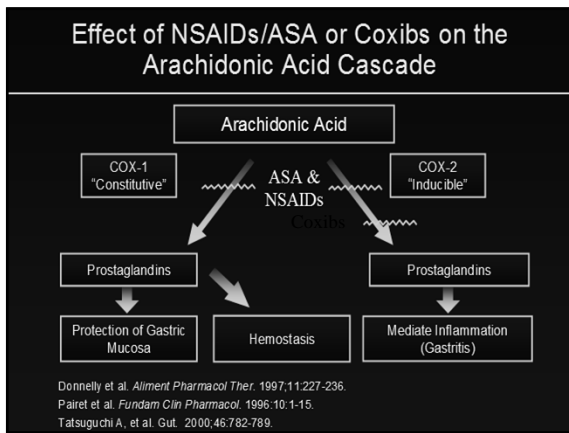
- Upper GI symptoms (up to 50%)
  - Heartburn, nausea, vomiting, pain
  - Frequent reason for stopping / changing NSAID
- Mucosal lesions [NSAID gastropathy] (up to 30%)
- Ulcer complications (up to 4% per year)
  - Bleeding, perforation, gastric outlet obstruction

### Enteric-coated or Buffered Aspirin Does Not Lower GI Risk

Risk of Upper GI Bleeding With Different Formulations of Low-dose Aspirin ( $\leq 325$  mg)

Bleeding Type	Plain Aspirin	Coated Aspirin	Buffered Aspirin
Gastric bleeding	2.6 (1.5-4.3)	3.2 (1.5-7.0)	3.6 (1.3-9.8)
Duodenal bleeding	2.4 (1.2-4.6)	2.6 (1.0-7.0)	2.6 (0.7-9.9)

• This case-control study included 550 patients with upper GI bleeding admitted to hospital with melena or confirmed hematemesis and 1202 controls  
Kelly JP, et al. *Lancet*. 1996;348:1413-1416.



### NSAID Ulcers: 1<sup>st</sup> Symptom Can be a Serious GI Complication

Symptom Status	Percentage
Without prior symptoms	19%
With prior symptoms	81%

Most patients are asymptomatic prior to having an NSAID-related ulcer bleed, perforation, or obstruction (i.e., Endoscope symptoms, prophylax risk)

Adapted from: Singh. *Am J Ther*. 2000;7:115. Singh et al. *Arch Intern Med*. 1996;156:1530.

### Lansoprazole and Misoprostol Provide Gastric Protection From NSAID Use

537 Long-term NSAID users with a history of gastric ulcer All *H. pylori* negative

Outcome	Misoprostol 800 µg/day	Lansoprazole 15 mg/day	Lansoprazole 30 mg/day	Placebo
Ulcer free at 12 weeks	93*	80*	82*	51
Experienced adverse effects	31*	7	16	10

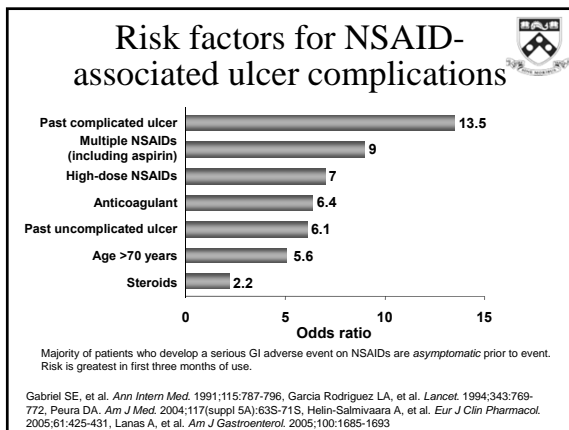
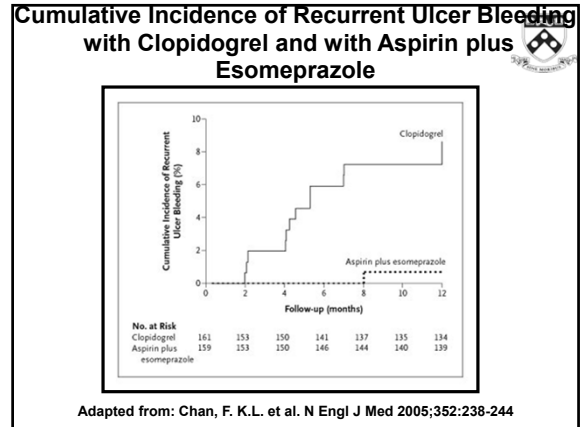
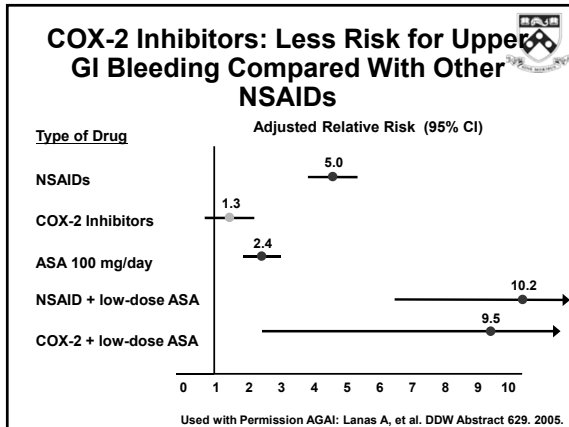
\* P < 0.001 vs. placebo  
Graham DY, et al. *Arch Intern Med*. 2002;162:169-175.

### Gastroprotection: Proton Pump Inhibitors

% of patients with recurrent upper GI bleeding at 6 months

Group	% of patients with recurrent upper GI bleeding at 6 months
<i>H. pylori</i> eradication + NSAID (n=75)	68.2
<i>H. pylori</i> eradication, Omeprazole + NSAID (n=75)	20.0

p=0.005  
76% RRR in upper GI bleeding; NNT = 7  
Adapted from: Chan et al. *N Engl J Med* 2001;344:967-973



### ACG Guidelines for the Prevention NSAID-related Ulcer Complications

GI Risk			
	Low (No risk factors)	Moderate (1-2 risk factors)	High (complication and/or >2 risk factors)
CV Risk Low	NSAID alone	NSAID+PPI/misoprostol	Alternative therapy or COX-2 inhibitor + PPI/misoprostol
CV risk High (ASA required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Alternative therapy and Avoid NSAIDs and COX-2 inhibitors

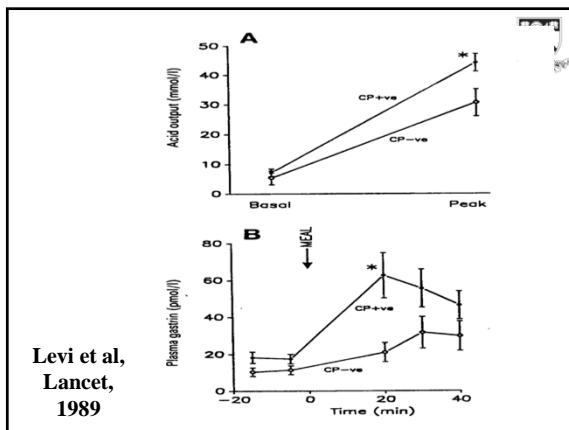
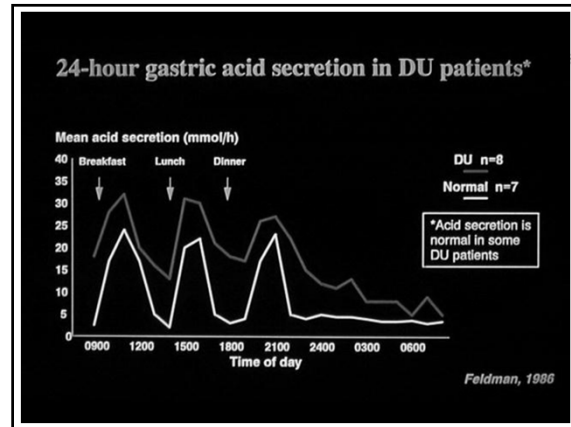
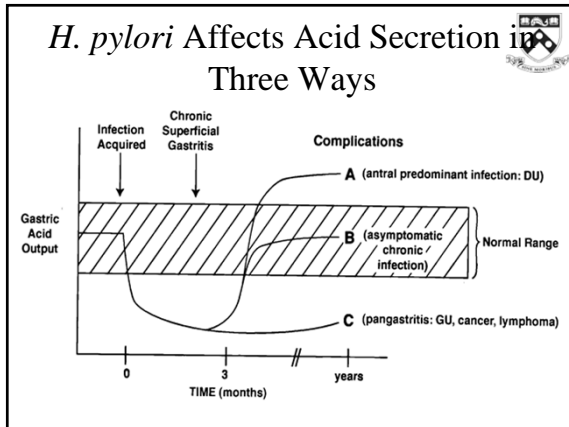
Note: Patients with a history of ulcers should also be tested for *H. pylori* and treated if positive

Adapted from: Lanza FL, et al. Am J Gastroenterol. 2009; 104:728-38.

### iii. *Helicobacter pylori*

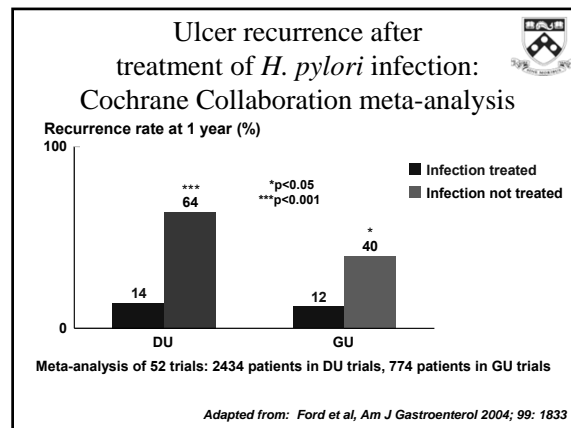
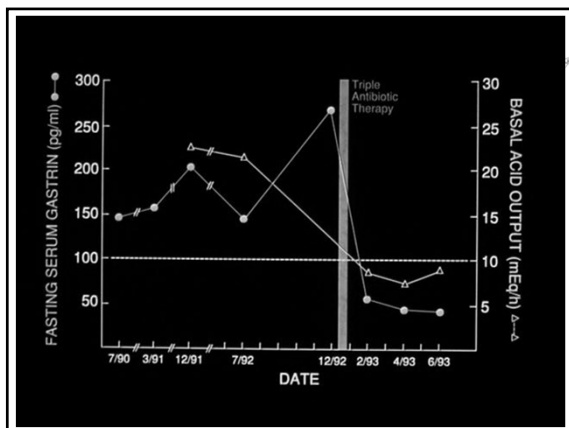
Peptic ulcer disease is an infection!

- ### The Spectrum of *H. pylori* Infection
- Chronic gastritis (Koch's postulate fulfilled)
  - Duodenal ulcer (up to 90%)
  - Gastric ulcer (about 70%)
  - Gastric cancer
    - Chronic gastritis → atrophy → intestinal metaplasia → dysplasia → cancer
  - Maltoma (lymphocytic gastritis)
  - Non-Ulcer Dyspepsia (?? Associated)



### *H. pylori* and Duodenal Ulcer: The Gastrin Hypothesis

- Antral *H. pylori* infection inhibits somatostatin production leading to unopposed gastrin release
- Basal and meal-stimulated hypergastrinemia lead to inappropriate gastric acid hypersecretion
- Duodenal gastric metaplasia (possibly due to hypersecretion or a primary phenomenon) permits colonization in the duodenal bulb
- Local defences are undermined PLUS acid hypersecretion results in duodenal ulceration



### Two Key Questions: PCN allergy; Prior macrolide exposure

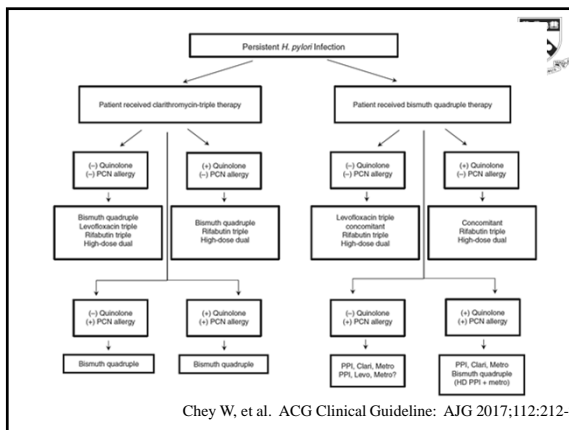
PCN allergy: No MCL exposure: No  Recommended treatments: Bismuth quadruple <b>CONCOMITANT</b> Clarithromycin triple With amoxicillin  Other options: Sequential <b>HYBRID</b> Levofloxacin triple Levofloxacin sequential LOAD?	PCN allergy: No MCL exposure: Yes*  Recommended treatments: Bismuth quadruple Levofloxacin triple  Other options: Concomitant therapy? Sequential therapy? Hybrid therapy? LOAD?	PCN allergy: Yes MCL exposure: No  Recommended treatments: Clarithromycin triple with metronidazole Bismuth quadruple	PCN allergy: Yes MCL exposure: Yes*  Recommended treatment: Bismuth quadruple
--	---	--	---

Chey W, et al. ACG Clinical Guideline: AJG 2017;112:212-238.

### Antibiotic Resistance rates in the USA 2009-2011

Antibiotic	Resistance rate (%)
Metronidazole	20
Clarithromycin	16
Levofloxacin	31
Tetracycline	<2
Amoxicillin	<2
Rifabutin	<2

Chey W, et al. ACG Clinical Guideline: AJG 2017;112:212-238.



### *H. pylori* gastritis and NSAID/ASA use often co-exist

Huang et al, Lancet 2002; 359: 14-22

### iv. Complications of Peptic Ulcers

- Bleeding
- Perforation
- Obstruction

### General Approach to the patient with Acute Upper GI Bleeding

- Guiding Principles
  - Restoration or maintenance of hemodynamic stability
  - Blood products if needed
  - Nasogastric lavage
  - Endoscopy with hemostasis if indicated
  - Antisecretory medications
  - Surgery if necessary

### GI Bleed: Prognostic Factors

- Initial assessment of an acute upper GI bleed can predict risk of mortality and complications:
  - Age >60 years
  - Transfusion requirement of >6 units of blood
  - Shock
  - Presence of comorbidity (hepatic, renal, pulmonary disease, cancer, CHF)
  - Ongoing bleeding
  - Low systolic blood pressure
  - Elevated prothrombin time
  - Erratic mental status
  - Major stigmata of recent hemorrhage

Silverstein FE, et al. *Gastrointest Endosc.* 1981;27:80-93.  
Rockall TA, et al. *Gut.* 1996;38:316-321.  
Kollef MH, et al. *Crit Care Med.* 1997;25:1125-1132.

### Management of Acute GI Bleeding

**Initial Management**

IV Access  
Hemodynamic Assessment  
CBC, PT/ PTT, LFTs, electrolytes/creatinine

Type and Cross  
Resuscitation Measures  
NPO

**Assess Initial Risk**

**High Risk**  
- Age >60 years  
- Comorbidity  
- Low systolic blood pressure

**Low Risk**  
- Shock  
- Ongoing bleed  
- Prolonged PT  
- Erratic mental status

ICU/Surgical consult → **Endoscopy ± Hemostasis** ← Med./Surg. Ward

Adapted from Greenspoon et al, CGH 10:2012:234-  
Adapted from Laine L, et al. *N Engl J Med.* 1994;331:717.

### Management of Acute GI Bleeding (cont'd)

**Endoscopy ± Hemostasis**

**Evaluate Risk for Rebleed**

**High Risk** (active bleed, visible vessel) → **Therapeutic Endoscopy** IV PPI ICU Surgical Consult

adherent clot

**Low Risk** (clean base, flat spot) → **Treat Underlying Ulcer** Oral PPI Ward (or even D/C)

Adapted from Greenspoon et al, CGH 10:2012:234-  
Adapted from Laine L, et al. *N Engl J Med.* 1994;331:717.

### Gastric ulcers presenting with acute upper GI bleeding

### GI Bleed: Risk of Rebleeding

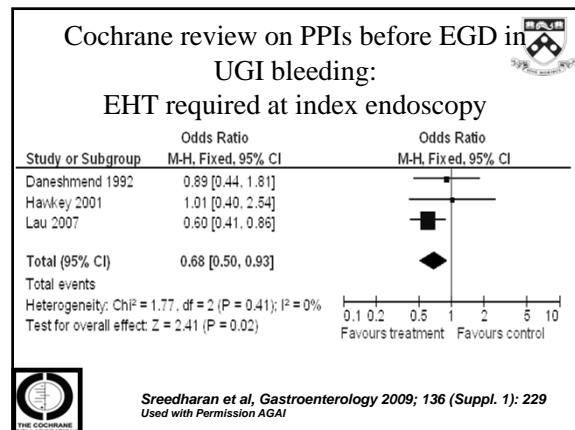
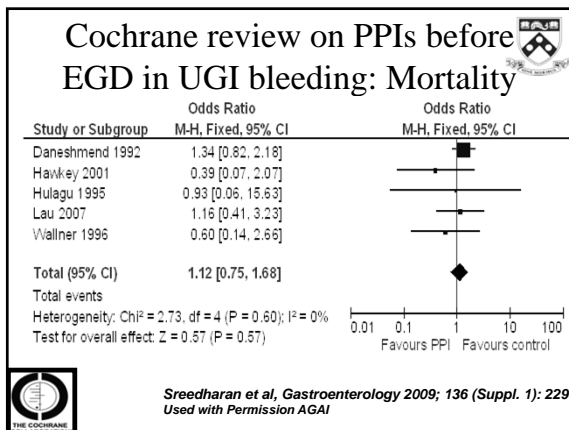
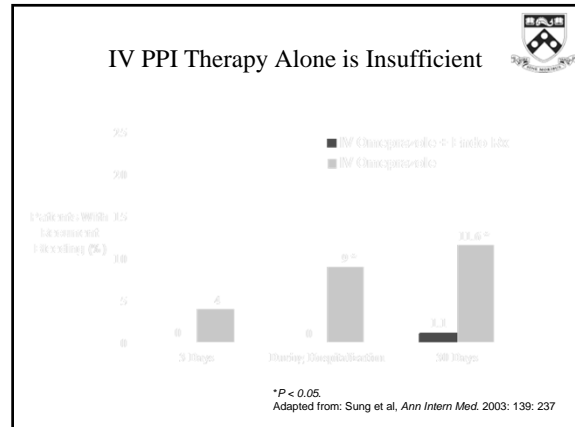
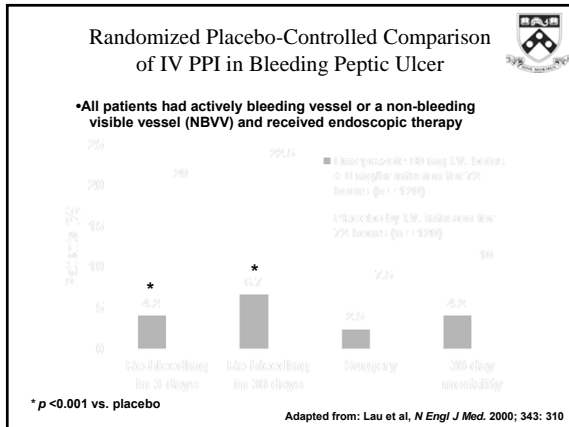
	Clean Base	Flat Spot	Adherent Clot	NBVV*	Active Bleed
Prevalence (%)	42	20	17	17	18
Rebleeding risk (%)	5	10	22 †	43 †	55 †
Mortality (%)	2	3	7	7	11

\*Nonbleeding visible vessel. † Endoscopic therapy recommended.  
Adapted from Laine L, Peterson WL. *N Engl J Med.* 1994;331:717-727.

### Endoscopic Hemostasis in Nonvariceal UGI Bleeding

- Thermal, laser and injection therapy all decrease rebleeding (OR 0.38), surgery (OR 0.36) and mortality (OR 0.55) in patients with active bleeding or visible vessels but not in those with flat spots or adherent clot
- Epinephrine + thermal methods or hemoclip
  - superior to epinephrine alone
  - not superior to thermal or hemoclip alone
- 2<sup>nd</sup> look endoscopy for rebleeding reduces the need for surgery without increasing complications

Cook et al. *Gastroenterology* 1992;102:139  
Marmo et al, *Am J Gastroenterol* 2007; 102: 279  
IK Chung et al. *Gastrointest Endosc* 1999; 49:13



### Management of Patients with Ulcer Bleeding: ACG Practice Guidelines\*

\*Lists 30 recommendations for pre and post endoscopic management of patients with ulcer bleeding including follow up to prevent recurrent bleeding

<i>H. pylori</i>	<i>H. pylori</i> Therapy	Document Cure Stop PPI/H2RA
NSAID	Stop NSAID	→ If NSAID required, use coxib+PPI
Low-dose aspirin	1. <b>Primary CV Prevention</b> Do not resume aspirin in most patients  2. <b>Secondary CV Prevention</b> Resume aspirin soon after hemostasis (e.g. 1- 7 days) in most patients and start PPI	
Idiopathic	Maintenance PPI	

Adapted from: Laine L and Jensen D. *Am J Gastroenterol* 2012; 107:345-60

- ### Conclusions
- PUD results from an imbalance between aggressive and defensive factors
  - The major causes of PUD are gastric acid hypersecretion, *H. pylori* infection and NSAID gastropathy
  - Complications include bleeding, perforation and gastric outlet obstruction.
  - Peptic ulcer bleeding requires risk stratification for ideal management