10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Peptic Ulcer Disease – How To Treat Today?

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Disclosures

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- Consultant: Takeda, Medtronic, Johnson & Johnson, Syneos, AstraZeneca, Intra-Sana Laboratories, Carnot, and Daewoong
- Advisory Board – Phathom Pharmaceuticals

Important Facts

- Two-thirds of patients with peptic ulcer disease are asymptomatic; those with symptoms most commonly experience epigastric pain.
- Most cases of peptic ulcer disease are associated with Helicobacter pylori infection or nonsteroidal anti-inflammatory drug use.
- Timely diagnosis and treatment of peptic ulcer disease is crucial

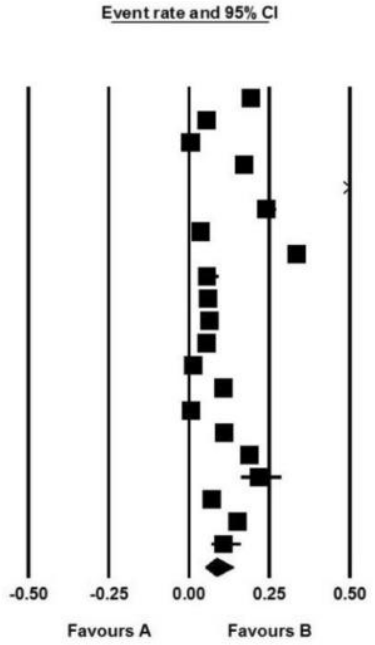
Definition of a Peptic Ulcer

- Peptic ulcer disease is often defined as a mucosal break greater than 3-5 mm in the stomach or duodenum with a visible depth.
- It is therefore an endoscopic diagnosis in contrast to dyspepsia, which is a clinical diagnosis based on symptoms alone

Epidemiology

- Globally – 8.4% prevalence of peptic ulcers

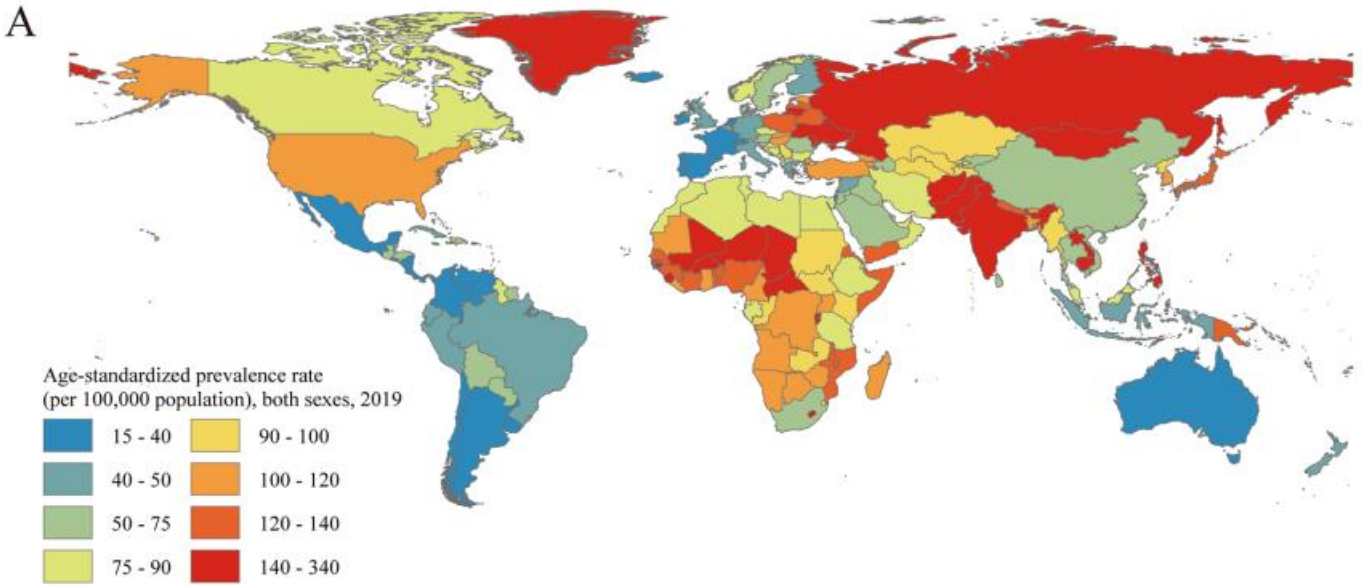
Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Kim, J. I.	0.192	0.187	0.196	96.299-	0.000
Kim, M	0.054	0.044	0.065	26.658-	0.000
Landau, D. A.	0.005	0.004	0.005	248.589-	0.000
Li, Z.	0.172	0.150	0.197	18.951-	0.000
Loffeld, R. J. L. F.	0.581	0.531	0.630	3.136	0.002
Malaty, H. M.	0.240	0.213	0.269	14.500-	0.000
Manfredini, R.	0.036	0.034	0.038	100.342-	0.000
Marques, S. B.	0.334	0.311	0.359	12.497-	0.000
McJunkin, B.	0.056	0.033	0.092	10.286-	0.000
Pyo, J. H.	0.060	0.057	0.062	117.711-	0.000
Ramirez-Ramos, A.	0.064	0.062	0.067	116.473-	0.000
Schabowski, J.	0.053	0.048	0.059	52.167-	0.000
Segawa, K.	0.014	0.012	0.016	53.526-	0.000
Sonnenberg, Amnon	0.108	0.105	0.111	133.449-	0.000
Sonnenberg, A.	0.005	0.005	0.006	101.964-	0.000
Türkdogan, MK	0.109	0.098	0.121	34.243-	0.000
Wong, S. N.	0.188	0.171	0.206	25.255-	0.000
Wroblewski, M.	0.218	0.162	0.286	6.884-	0.000
Wu, H. C.	0.071	0.069	0.073	155.324-	0.000
Xia, B.	0.150	0.137	0.164	32.184-	0.000
Yeomans, N. D.	0.107	0.070	0.160	8.969-	0.000
	0.084	0.050	0.137	8.561-	0.000



Prevalence of peptic ulcer in the world and 95% confidence interval

Salari N et al. *Indian Journal of Surgery.* October 2022. 84(5):913–921.

The Age-Standardized Prevalence Rate (Per 100,000 Population) in Both Sexes Globally in 2019.



Xie et al. *BMC Gastroenterology*. 2022. 22:58.

Main Etiology

Helicobacter pylori infection	Significantly more common in developing nations May lead to both gastric and duodenal ulcers
Nonsteroidal antiinflammatory drugs	Includes acetylsalicylic acid (ASA) More commonly associated with gastric ulcers
Other medications	Co-administration of corticosteroids and bisphosphonates with NSAIDs; Sirolimus, selective serotonin reuptake inhibitors (SSRIs), 5-fluorouracil (5-FU)
Smoking	Synergistic effect between tobacco use and *H. pylori* infection
Neoplasms	Gastrinoma, gastric adenocarcinoma, carcinoid syndrome
Idiopathic	No cause identified despite thorough investigation

NSAID = nonsteroidal antiinflammatory drug.

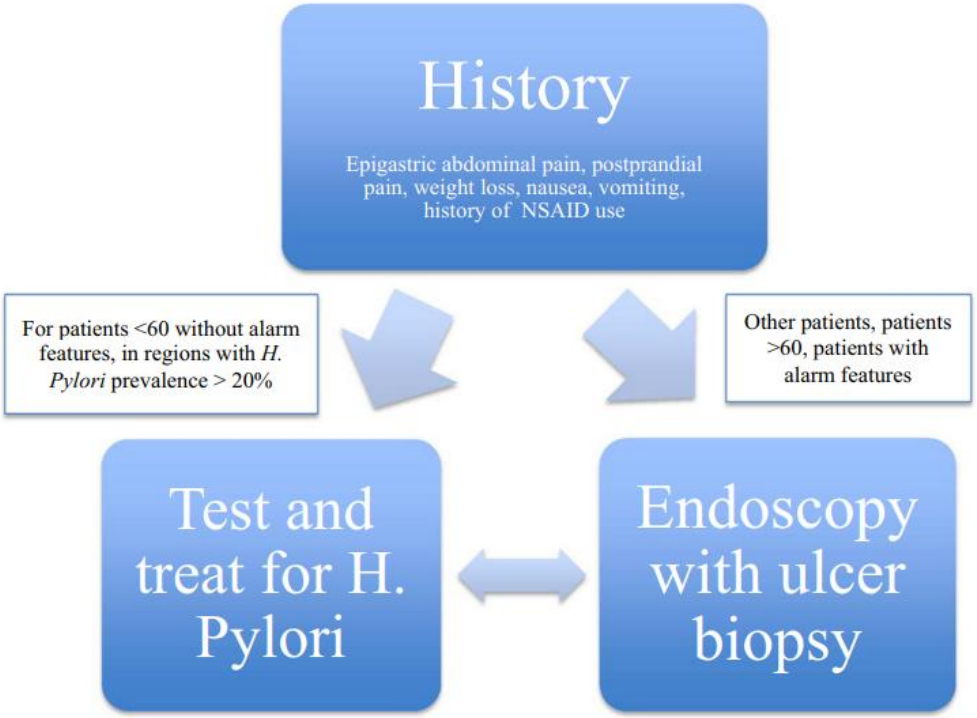
Kavitt R et al. *Am J Med*. 2019. 132:447−456.

Other Etiology

- Gastric adenocarcinoma
- Gastric lymphoma
- Local drug irritation
- Cameron’s lines (ulcers)
- Idiopathic
- Anastomotic ulceration
- After radiotherapy
- Zollingere Ellison syndrome (gastrinoma)
- Multiple endocrine neoplasia type-I
- CMV, TB and syphilis
- Hyperparathyroidism
- Systemic mastocytosis
- Severe systemic illness stress ulcers (Cushing’s ulcer)
- Idiopathic eosinophilic and lymphocytic gastritis
- Duodenal Crohn’s disease
- Coeliac axis stenosis
- Hepatic artery chemotherapy
- Vasculitis, sarcoidosis

Jaiswal F et al. *Asian J Pharmaceutical Edu Res*. 2021; 10(4): 01-17.

Diagnosis



Kavitt R et al. *Am J Med*. 2019. 132:447–456.

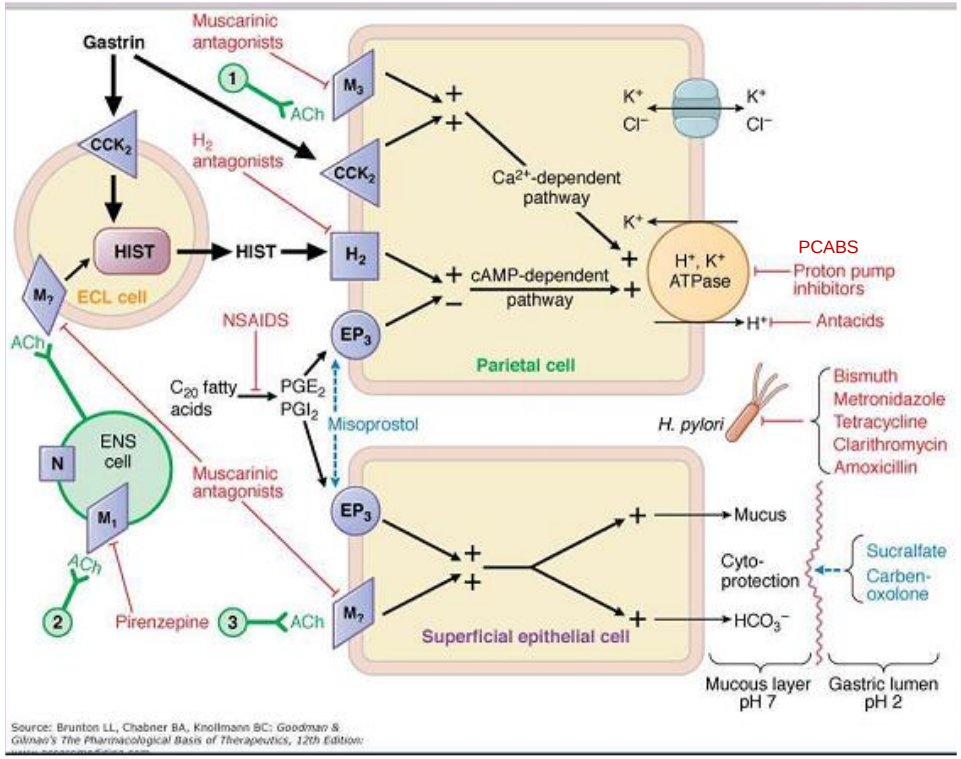
Non-Complicated PUD – First Step

- H. Pylori positive – Eradicate and confirm eradication
- NSAIDS/Aspirin consumption – Discontinue and reassess the need for one or both

Medical Therapy for PUD

- Anti-secretory Medications
  - H2RA
  - PPI
  - PCABs
- Mucosal protectants
  - Misoprostol
  - Sucralfate
- Anti – cholinergics
  - Add on Glycate (Glycopyrrolate)

Regulation of Gastric Acid Secretion and Location of Drug Effects



PPI Doses in Active Therapy of Uncomplicated PUD

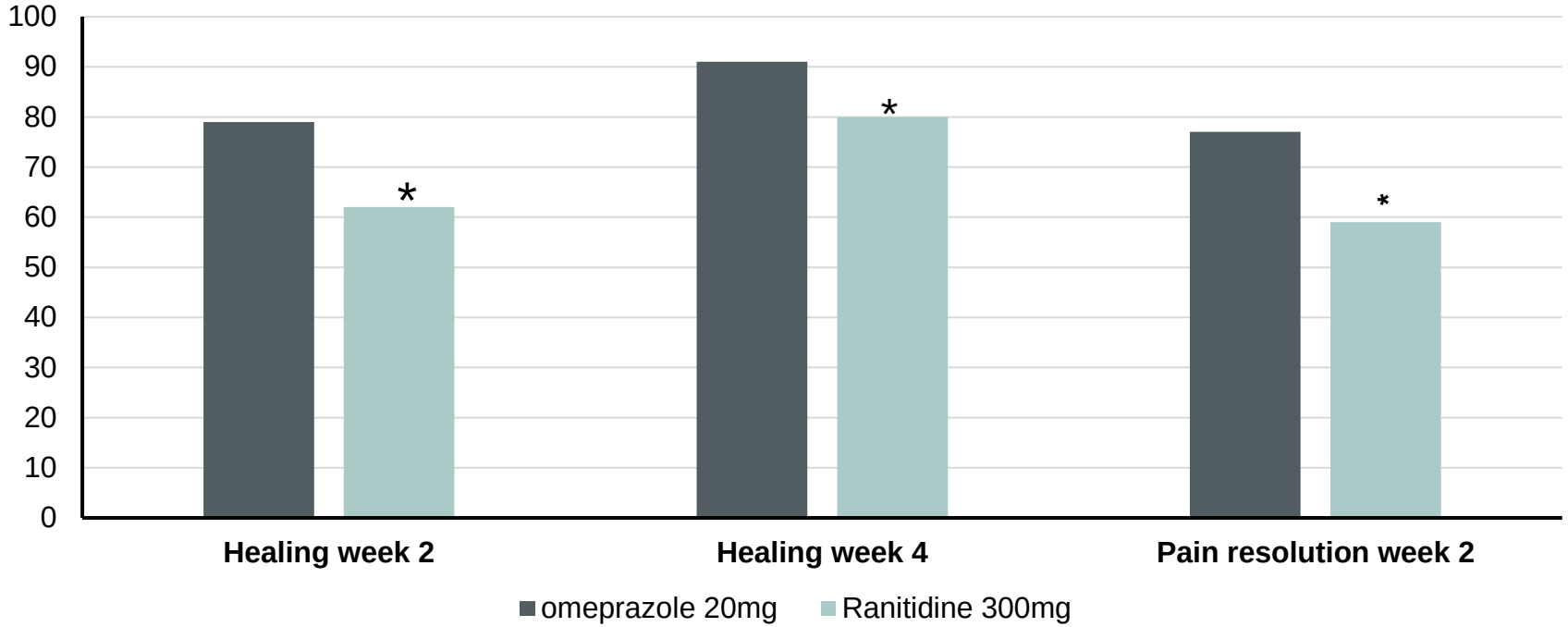
Drug	Dose (adult)
Dexlansoprazole	30 to 60 mg
Esomeprazole	20 to 40 mg
Lansoprazole	30 mg
Omeprazole	20 to 40 mg
Pantoprazole	40 mg
Rabeprazole	20 mg
All administered by mouth daily before breakfast	

Duodenal ulcer – 4-6 weeks of treatment

Gastric Ulcer – 6–8 weeks of treatment

Wolfe MM, Sachs G. *Gastroenterology.* 2000; 118:S9; Vakil N. *Uptodate*.

Omeprazole Versus Ranitidine in Healing and Controlling Symptoms of Patients With Duodenal Ulcer



* p<0.05

McFarland RJ et al. *Gastroenterology.* 1990 Feb;98(2):278-83.

Repeat Endoscopy for Ulcer Healing Assessment

- Persistent symptoms or recurrent symptoms after discontinuation of PPI therapy
- Complicated ulcer (bleeding) with evidence of ongoing bleeding
- Giant gastric ulcer (>2 cm)
- Ulcer with features of malignancy at index endoscopy
- Gastric ulcer that was not biopsied or inadequately sampled on the index upper endoscopy (4 biopsies from four quadrants of the ulcer and additional biopsies if needed)
- Gastric ulcers in a patient with risk factors for gastric cancer
- Gastric ulcer of unclear etiology

Complications of PUD

- Bleeding, perforation, penetration, and gastric outlet obstruction.
- Risk factors - NSAIDs including aspirin, H. pylori infection, smoking, and Zollinger-Ellison syndrome.
- Ulcer specific characteristics - chronicity/refractory type ulcers, large size (≥1 cm), and location (e.g., pyloric channel)
- Factors associated with poor outcome include concomitant comorbid disease, older age, poor physiological status at the time of presentation (eg, hypotensive shock, metabolic acidosis, acute renal failure, hypoalbuminemia), and delayed treatment.

Acute Upper Gastrointestinal Hemorrhage – The Most Common Complication of Peptic Ulcer Disease

- Mortality up to 10%
- Upper endoscopy is the best initial test (diagnostic and therapeutic).
- Endoscopic hemostasis therapies include injection, thermal, mechanical, or a combination of them
- Endoscopic hemostasis has been shown to be effective in achieving primary hemostasis and to significantly reduce ulcer re-bleeding, need for blood transfusion, urgent surgery, length of hospitalization, and mortality.
- High-dose intravenous PPIs should be used for 72 hours post endoscopic hemostasis followed by oral PPI therapy.

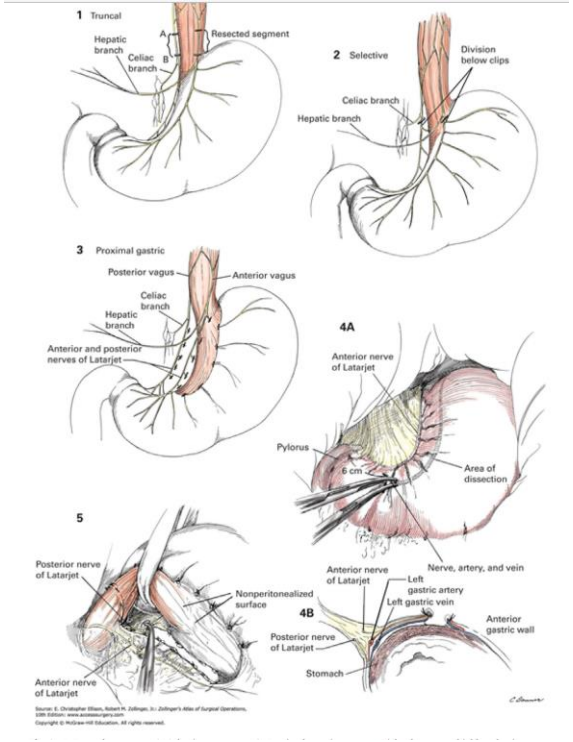
Kavitt R et al. *Am J Med*. 2019. 132:447–456.

After Endoscopy

- If high-risk stigmata is present on endoscopy, treat with high-dose intravenous PPI for 72 hours
- Repeat endoscopy if there is evidence of recurrent bleeding
- Refer to surgery or interventional radiology if there is rebleeding after second endoscopic therapy
- Closely assess need for NSAIDs in those with NSAID-associated ulcers
- Treat for Helicobacter pylori infection if applicable
- Continue long-term PPI therapy in those with idiopathic peptic ulcers

Kavitt R et al. *Am J Med*. 2019. 132:447–456.

Surgical Treatments for PUD



Wang A et al. *Current Problems in Surgery.* 57 (2020) 10072.

ACG Guidelines: Assessing the Risk of NSAID-Induced GI Toxicity

- **Risk factors include**
  - Age >65 years
  - High-dose NSAID therapy
  - History of ulcer
  - Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants

LOW RISK
- No risk factors

MODERATE RISK
- 1–2 risk factors

HIGH RISK
- >2 risk factors
- History of complicated ulcer

Just one risk factor, such as high-dose NSAID use, puts a patient at moderate risk for an upper GI ulcer.

 Lanza FL et al. *Am J Gastroenterol*. 2009;104(3):728-738.

Indications for Long Term Therapy With a PPI in Long Term Users of Aspirin or NSAIDs

- Age >65 years
- A history of peptic ulcer disease, especially with complications
- NSAID use at high doses or in combination with certain other drugs, ie, aspirin, steroids, selective serotonin reuptake inhibitors, or anticoagulants
- Aspirin use, even at low dosage in elderly patients, particularly in combination with the drugs listed above

Sverden E et al. *BMJ*. 2019;367:l5495 .

Refractory Peptic Ulcer

- Definition — Endoscopically proven ulcer greater than 5 mm in diameter that does not heal after 8 to 12 weeks of treatment with a proton pump inhibitor
- Prevalence – 5%–10% of the treated ulcers

Causes of Refractory Peptic Ulcer

Causes of refractory gastric/duodenal ulcers

Persisting *H. pylori* infection
Poor compliance with treatment
Resistant organism
Inadequate *H. pylori* regimen
Unrecognized *H. pylori* infection:
False negative *H. pylori* testing
Skipped or inadequate testing
Ulcers related to nonsteroidal anti-inflammatory drugs (NSAIDs)
Continued NSAID use
Undiscovered NSAID use
Poor response to co-therapy with a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA)
Other mechanisms
Impaired healing:
Cigarette smoking
Inadequate inhibition of acid secretion:
Poor compliance with treatment
Pharmacologic resistance or tolerance to H2RAs
Pharmacologic resistance to PPIs
Rapid metabolism (inactivation) of PPIs
Hypersecretory states:
Gastrinoma
Antral G cell hyperfunction
Idiopathic hypersecretory duodenal ulcer
Co-therapies:
Glucocorticoids (especially when given with NSAIDs)
Cytotoxic drugs
Other drugs, such as methamphetamine or cocaine use
Uncommon causes:
Cancer
Crohn disease
Infections other than *H. pylori*
Eosinophilic, inflammatory, infiltrative conditions, mesenteric ischemia

Need for Long Term Acid Suppression

- Persistent ulcer on repeat endoscopy
- Giant (>2cm) ulcer and age >50 years or multiple comorbidities
- Recurrent peptic ulcer (>2 a year)
- Need for long term aspirin/NSAID use
- Failure of repeated attempts of H. Pylori eradication