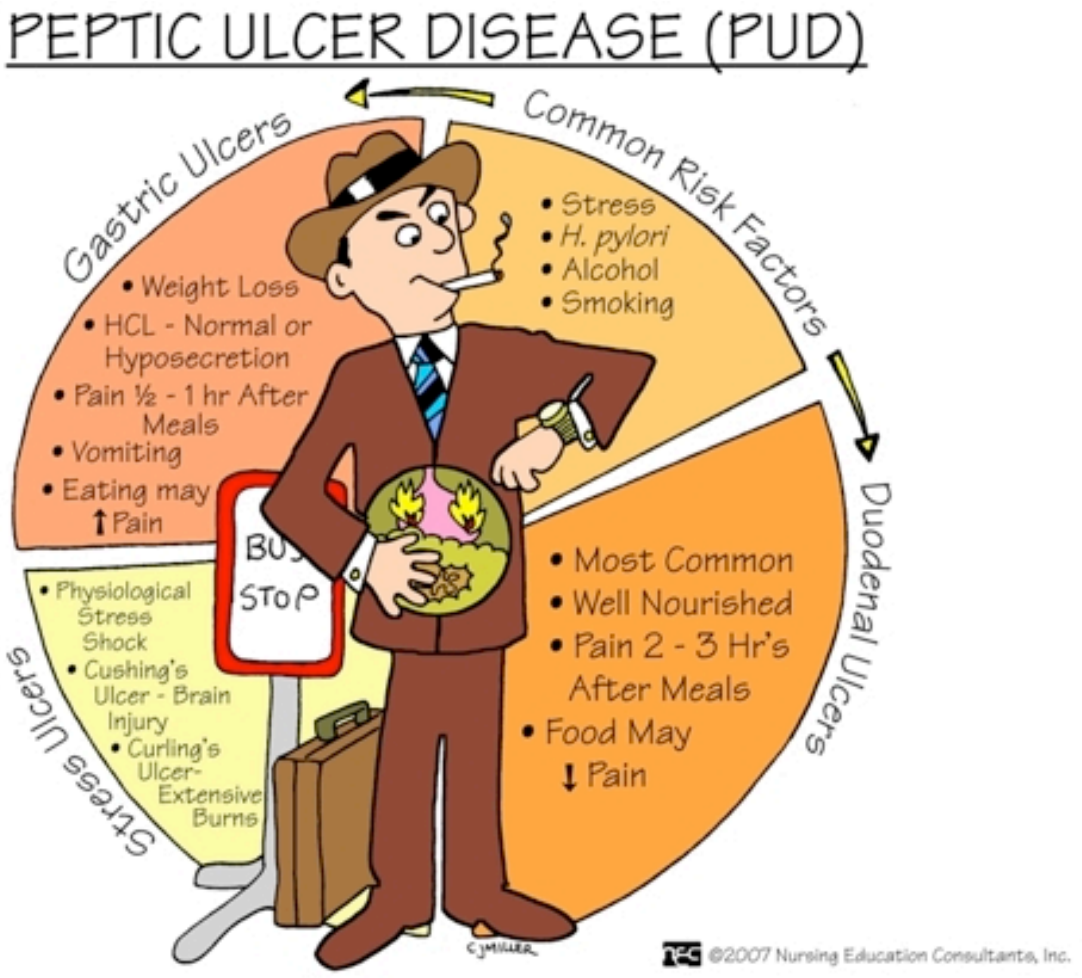
Drugs Used For Peptic Ulcer

(H2- Blockers and Proton Pump Inhibitors)



Pharma Team

Team notes are in boxes and/or in red

First two pages, we will introduce the disorders of which we will discuss its treatment.

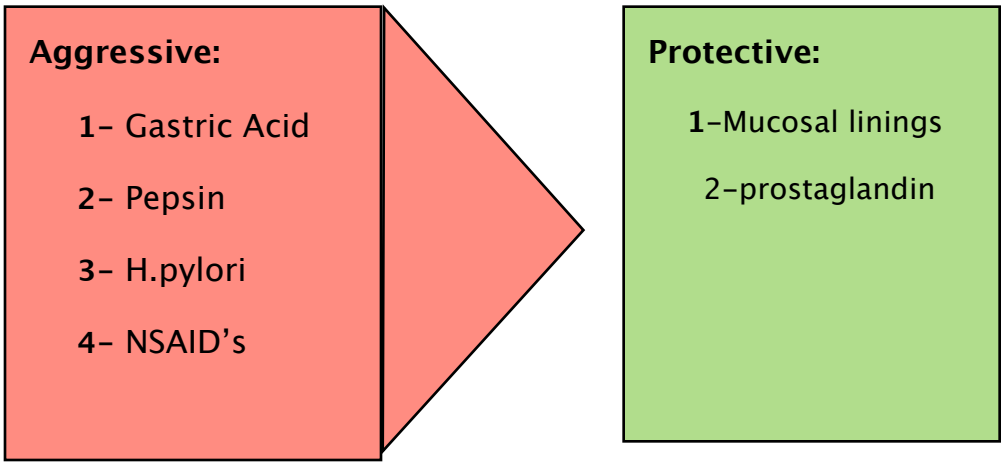
Peptic Ulcer Disease and GERD

· Peptic ulcer disease,

- Occurs in stomach or the duodenum (mainly)

- **Pathophysiology:**

  We have an imbalance between aggressive and protective factors in the stomach:



- Our goal is to reduce the pain, heal the ulcer, and prevent its recurrence. We can do that by enhancing the protective factors or inhibiting the aggressive factors.

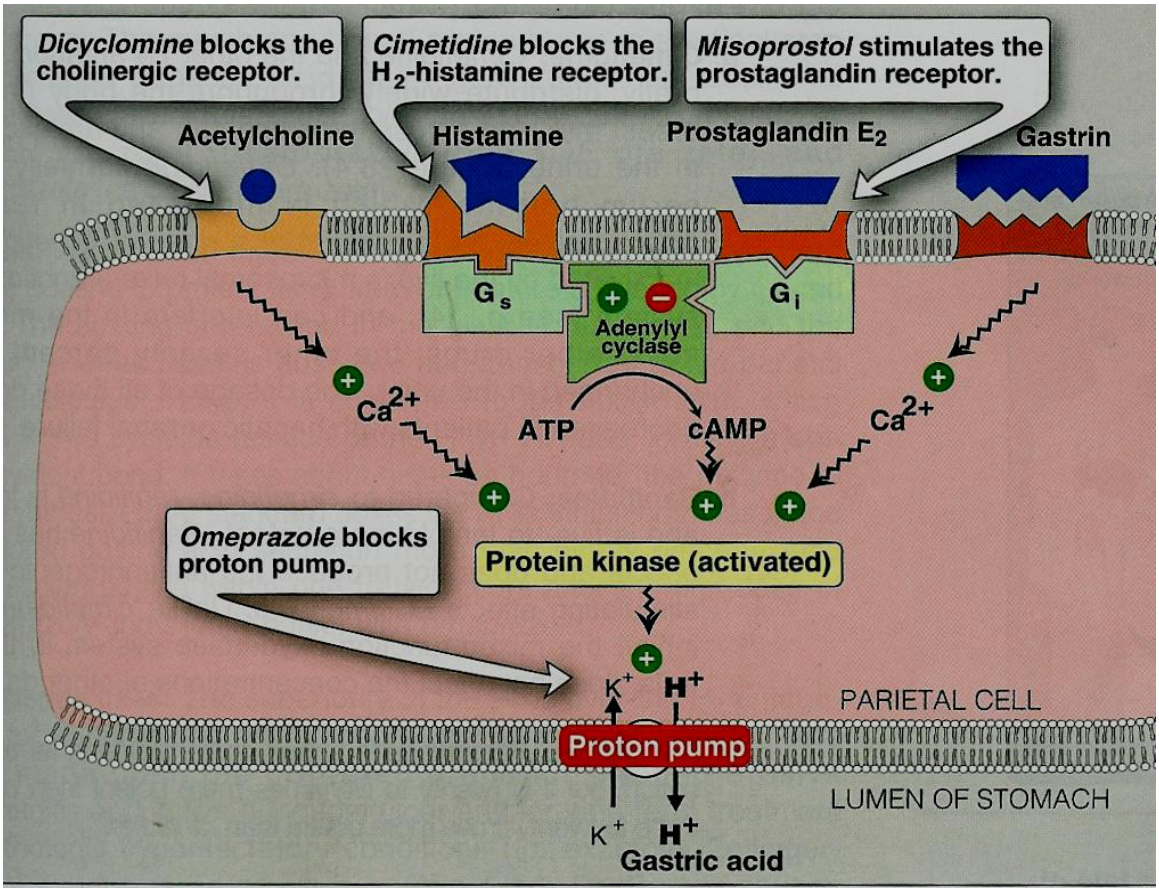
- To prevent further ulceration we need to eradicate (kill) the underlying bacteria (H. Pylori)

· GERD: Gastro-esophageal Reflux Disease

- Occurs when acid goes back (regurgitates) into the esophagus.
- **Treatment:**
  - Decrease gastric acidity (H2 blockers or PPIs.)
  - Increase tone of lower esophageal sphincter and increase gastric emptying

* Metoclopromide (prokinetic) is used to increase gastric motility and emptying -> Used in GERD

  - Avoid drugs or foods that trigger GERD.



Treatment methods

- **Currently used:**

  1- Antacids

  2- Anti-secretory drugs

  a. H_2 -receptor antagonists

  b. Proton Pump Inhibitors (PPI)

  3- Antibiotics for eradication of H.pylori (MAIN)

- **Less used:**

  1- Mucosal cytoprotective agents:

  a-Sucralfate

  b-Prostaglandin analogues c-Colloidal bismuth

  2-AcetylCholine Antagonists

* Prostaglandins analouges (Misoprostol) : are not used because of their unwanted actions in other regions of the body -> abortion and colics (pain)

* ACh antagonists have very low contribution to the treatment (only 5% reduction in Acid secretion)

1st) Antacids: "Organic salts"

- They are weak bases that attach to the "increased" acids in the stomach to Increase the PH.
- Examples: Aluminum and magnesium hydroxides
- Sodium bicarbonate and calcium carbonate

General:

- Over the counter ---> no prescriptions
- Low efficacy ---> less commonly used
- Work as a buffer system

- **MoA:** (Antagonize acid; Also, Indirectly may decrease pepsin activity)

*Pepsin (enzyme) cannot work in pH higher than 4.

- **Side Effects:**
  - **With aluminum hydroxide ---> Constipation**
  - **With magnesium hydroxide ---> Diarrhea**
  - **Milk alkali syndrome**

* Note: They are less commonly used because they are cost effective and better treatment is at hand. (PPI and H2 Blockers)

2nd) Anti-secretory drugs:

A- H_2 antagonists

General:

- High efficacy
- Less potent than PPI
- Safe drugs, given oral or IV.

Cimetidine
Ranitidine
Famotidine
Nizatidine

- **MoA:** They competitively & **reversibly** bind to **H2-receptors** on the parietal cells, thus decreasing the production of acid by these cells.
  (decreased cyclic AMP leads to decreased activity of H/K proton pump)

- **Pharmacological actions of H2 blockers:**

1. Reduce basal & food-stimulated gastric secretion.
2. Reduce acid secretion by 60% stimulated by histamine, as well as by gastrin & cholinergic drugs.
3. Reduce pepsin activity.(pepsin works in pH <4 only)
4. Block 90% of nocturnal acid secretion (which depend largely on histamine) & 60-70% of total 24 hr acid secretion.

*histamine-2 blockers should be given at night prior to the release of histamine to block it efficiently.

- **Pharmacokinetics:**

-Good & rapid oral absorption
-Plasma half life >> (1-4 hr).
-Duration >> (4-12 h).
-Given before meals.
-First pass (50% bioavailability Except Nizatidine 100%)

-Clearance by hepatic metabolism, glomerular filtration & renal tubular secretion

-SO Dose reduction is required in patients with moderate-severe renal (or severe hepatic) insufficiency.

-50% clearance decline in elderly -Cross placenta & excreted in milk.

	CIMETIDINE	RANITIDINE	FAMOTIDINE	NIZATIDINE
Efficacy	+++	++ +	+++	+++
Potency	+	++	+++	++
Dose	400 mg bid	150 mg bid	20mg bid	150 mg bid
Route	orally, IV	orally, IV	orally, IV	orally
T 1/2	short (2 h)	longer (3h)	longer (3h)	shortest (1
Duration	5-6 h	10 h	12 h	11 h
CYT P 450	++	-	-	-
Antiandrogenic	++	-	-	-
Drug interactions	many	No	No	No

Interpretation of figure:

- All H_2 antagonists have equal efficacy but with different potencies:

Efficacy: Cimetidine= Ranitidine= Famotidine

Potency:

Cimetidine< Ranitidine < Famotidine

- Cimetidine differs from the others in that it inhibits Cytochrome P450 >> decrease the metabolism of other drugs & prolong their $t_{1/2}$ (drug interactions) (E.g. with warfarin ---> prolongs bleeding time)

- Cimetidine also has antiandrogenic effects and consequently more ADR's than Ranitidine.

Antiandrogenic effects = effects related to sex hormones

• Side Effects:

1.CNS effects:

-Headache, confusion, hallucination & agitation due to IV H2 antagonists (more with cimetidine) but not with Ranitidine.

*Cimetadine when given as tablets causes sedation

2. Endocrine effects (Only by Cimetidine)

-Increases in serum prolactin (Galactorrhea in women)

-Inhibits binding of dihydro-testosterone to androgen receptors (gynecomasteia – impotence).

3. **All cross placenta & breast milk, should not be given in pregnancy unless urgent. (Not contraindicated)**

4. **Leucopenia and thrombocytopenia and headache**

*Leucopenia and thrombocytopenia = mainly with Ranitidine

5. **Bradycardia & hypotension (rapid I.V)**

-H2 antagonists compete with creatinine & certain drug (procainamide; antiarrhythmic) for renal tubular secretion.

- **Clinical Uses:**

1- GERD (heartburn/ dyspepsia).

2- PUD: effective in nocturnal acid suppression & ulcer healing in moderate cases.

3- Zollinger Ellison Syndrome (large doses).

4- Prevention of bleeding from stress-related gastritis.

5- Decrease the heartburn caused by NSAIDs.

b- Proton Pump inhibitors

They work by inhibiting the H/K atpase pump Directly and thus decrease Gastric acid secretion.

General:

- High efficacy & potency(more potent than H2 blockers)
- Irreversible ---->(up to 24 hr) & the effects may last up to 3 days
- Safe drugs
- Work directly to inhibit Gastric Acid release
- They cause complete Alkalization

Omeprazole
Lansoprazole
Pentoprazole
Raprazole
Esomeprazole

• MoA:

- **Irreversible** inhibition of **proton pump (H^+/ K^+ ATPase)** that is responsible for final step in gastric acid secretion from the parietal cells.
-24 hr inhibition of basal & meal stimulated-acid secretion (90-98%)

• Pharmacokinetics:

- They are prodrugs

* PPIs should not be used together with H2-antagonists or antacids because H2 antagonists and antacids will decrease the acidity, and PPI's are prodrugs that can be activated only when protonated(in acidity).

-All are taken orally **EXCEPT** Esomeprazole & Pantoprazole are also available in IV formulation.

- They are rapidly absorbed from the intestine & converted to active form.

-Given 1 h before meal; on empty stomach.

-Bioavailability is reduced by food (50%).

-Are metabolized in the liver by CytP450 >> SO Dose reduction is required in severe liver failure.

• Clinical Uses:

1- **Zollinger Ellison syndrome (1st choice).**

2- **PUD (4-8 weeks); faster & long- lasting ulcer relief.**

3- **GERD.**

4- **Prevention of bleeding from stress-related gastritis.**

5- **H. pylori-associated ulcer & NSAID-associated ulcer.**

• Side effects:

– Headache, diarrhea, nausea, decrease gastric acid secretion lead to hypergastermeia, and mucosal hyperplasia.

*hypergastermeia by mucosal hyperplasia of G cells and increased production of gastrinand hypochlorydia (achloria)

Chronic use:

– Vitamin B12 levels decrease.

–increased tendency for fractures (osteoporosis)

– Increased rate of infection due to low pH

–in animals it causes

carcinoid tumors (not in humans!)

* because acidity kills any bacteria in the stomach… H.pylori is not killed because it equalize the acidity by ammonia----> increased risk of both community-acquired respiratory infections & nosocomial pneumonia.)

H. Pylori Eradication

-it Is a bacteria that causes chronic inflammation of the inner lining of the stomach.

-Duodenal ulcer -Gastric ulcer

- Produce enzymes (tissue damage)

-Risk factor for gastric cancer.

-Eradication is important to prevent recurrence of ulcer.

- Treatment by triple therapy

-The best treatment regimen: Triple therapy (7-10 days)

-PPIs bid (any PPI can be used)

-Clarithromycin, 500 mg bid

-Amoxicillin, 1 g bid

* PPI's treatment should not exceed 14 days.