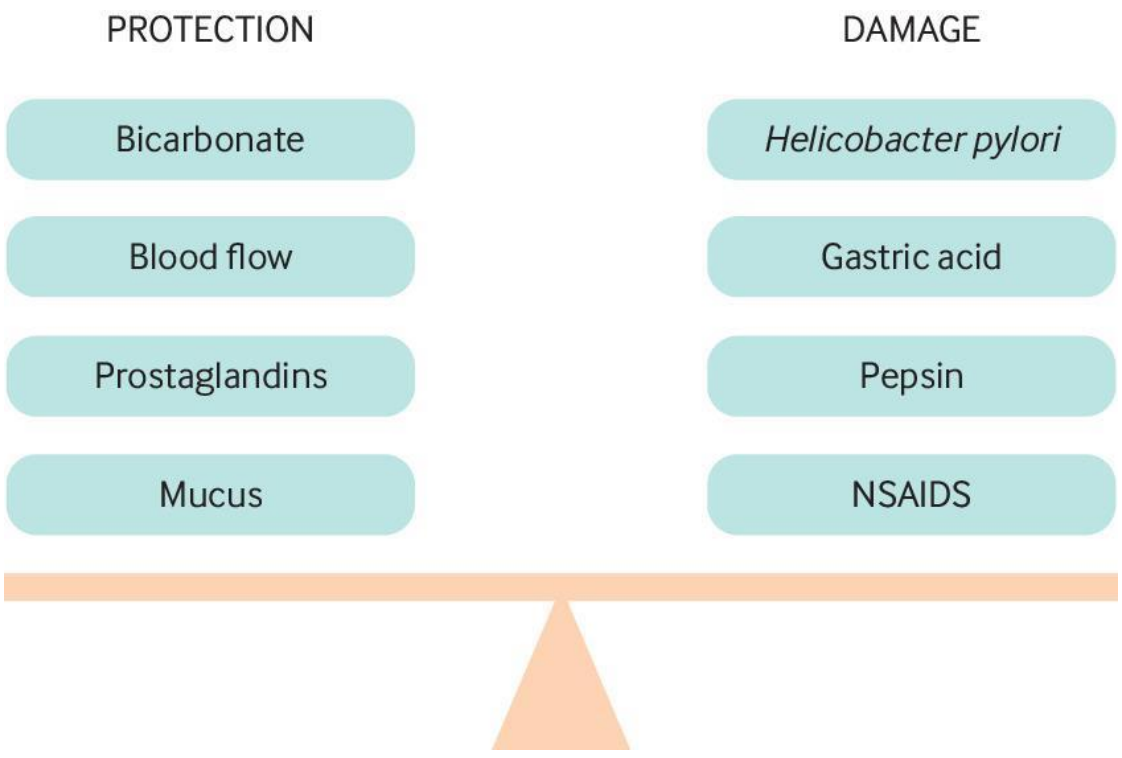
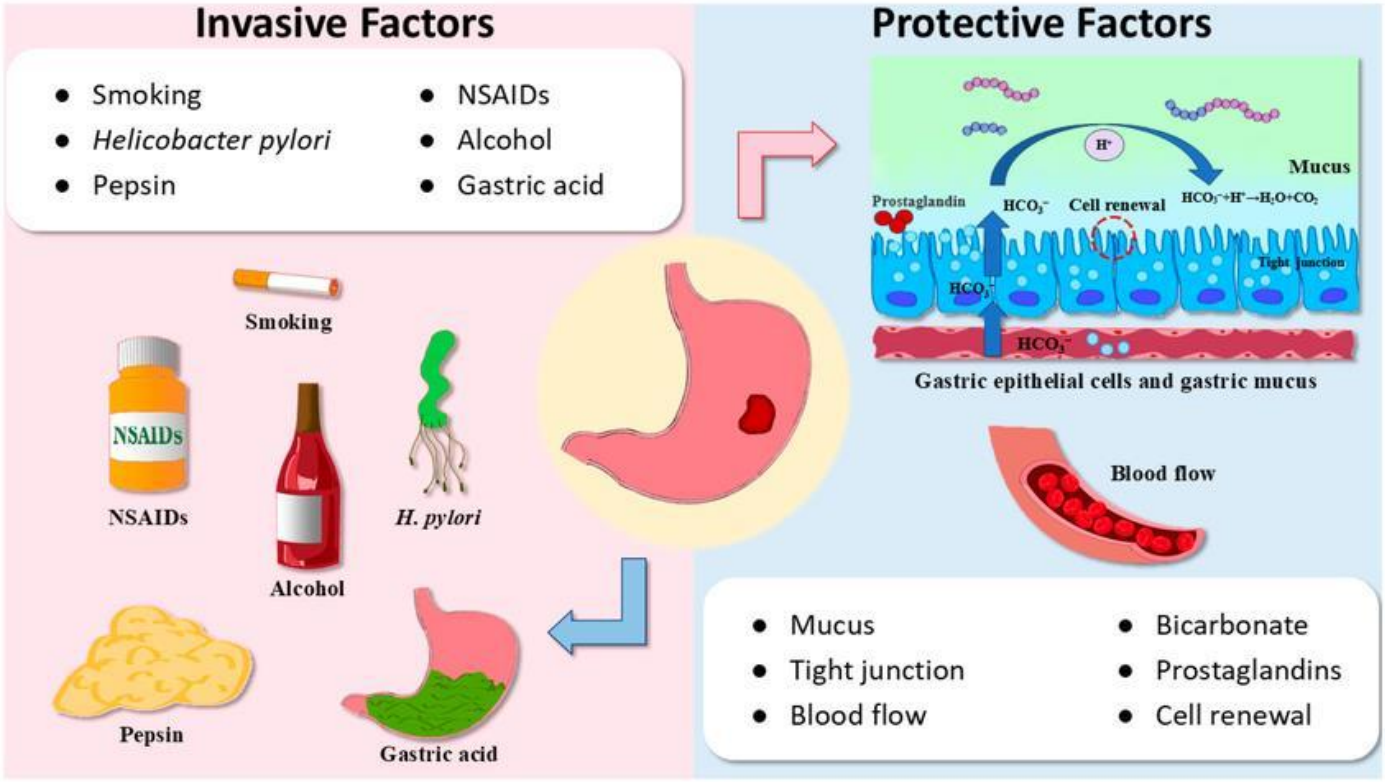
Treatment of Peptic ulcer

- ***Definition:***
  - ***ulceration*** *of the duodenum or stomach due to* ***imbalance between*** *local invasive force (e.g. HCl and pepsin) and protective mechanisms.*

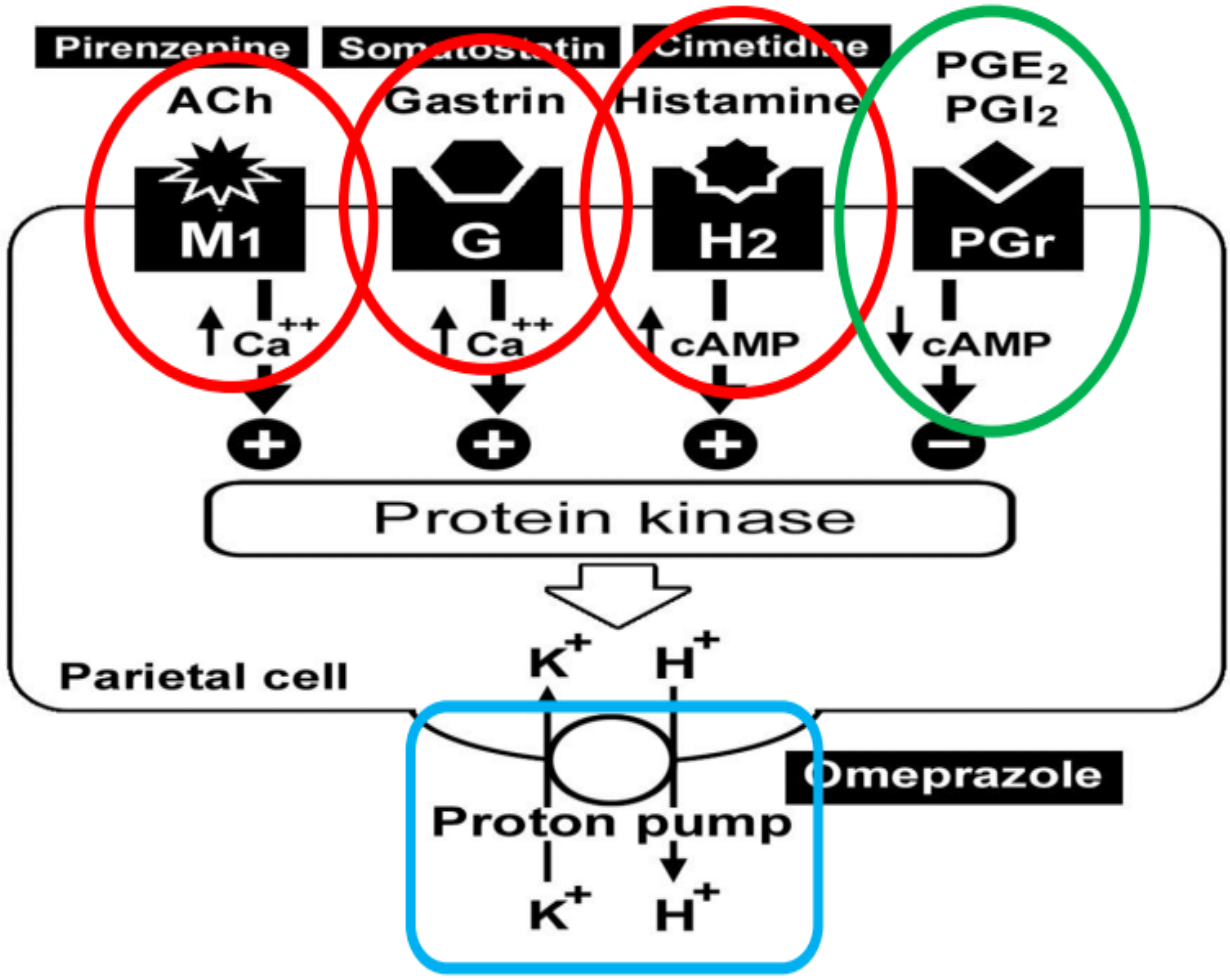
- ***Pathophysiology:***

Invasive factors:	*Defensive mechanisms:*
• ***Stress:*** *↑ HCl & pepsin secretion by parietal cells.* • ***Diet:*** *coffee, alcohol and spices.* • ***Bile reflux.*** • ***Drugs:*** ➢ *NSAIDs, corticosteroids, nicotine, morphine, methylxanthines, etc.* • ***Infection with Helicobacter pylori.***	• ***Mucus*** *production by gastric mucosa.* • *Local* ***PGE2 and PGI2*** *production.* • *Pancreatic* ***bicarbonate*** *secretion.* • *Good mucosal* ***blood flow.***





- ***Gastric partial cell:***



Therapy of peptic ulcer

A. Non-drug therapy = life style modification

- ***Rest and Sedation***
- ***Stop Smoking, Spices, alcohol, coffee, and tea.***
- ***Avoid Stress.***
- ***Avoid ulcerogenic drugs.***
- ***Diet:***
  - *Frequent **small meals** in DU in order to buffer high acidity.*

B. Pharmacological therapy:

Drugs neutralize HCl :	• *Antacids.*
Drugs ↓ HCl:	• ***Selective M1 blockers:*** *pirenzepine,.* • ***H2 blockers:*** *cimetidine, ranitidine, famotidine.* • ***Proton pump inhibitors:*** *omeprazole.* • ***Potassium Competitive Acid Blockers:*** *Vonoprazan*
Drugs ↑ mucosal defense:	• *Sucralfate* • *Colloid bismuth compounds* • *Carbenoxolone* • *PGE1 analogues: misoprostol.*
Anti-microbial drugs for H. pylori :	• *See later*

1- Antacids

- **Def:**
  - ***weak bases*** *that are taken orally and* ***partially neutralize*** *gastric acid and reduce pepsin activity.*
  - *They are used as* ***symptomatic relief*** *of hyperacidity and should not be used as* ***long-term treatment.***

- **Examples:**

	Sodium bicarbonate	Calcium carbonate	(Mg hydroxide & Aluminum hydroxide)
MOA	• *It can be absorbed systemically leading to* ***salt & water retention & metabolic alkalosis.***	• *Partially* ***absorbed*** *antacid.* • *Ca2+ may act directly to stimulate gastrin secretion leading to* ***acid rebound.***	• *They are* ***poorly absorbed*** *and have no systemic effects.* • *The unabsorbed Mg salts cause* ***osmotic diarrhea****; the unabsorbed Al salts cause* ***constipation.***
Contra-indication	• *It is contraindicated in* ***hypertension and heart failure.***	• *It is contraindicated in* ***hypercalcemia and renal stones.***	
Onset & duration	• *It has rapid onset and short duration.*		• *They have slow onset*

- ***Adverse effects:***

  a) Change in bowel habits:

  - *Al3+ hydroxide causes* ***constipation***
  - *while Mg2+ hydroxide cause* ***diarrhea.***
  - *Combination* ***solve*** *the problem.*

  b) Cation absorption (Na, Ca):

  a) Increase Ca++ *leads to systemic hypercalcemia with formation of calculi especially in renal impairment.*

  b) Increased Na+ *absorption leading to hypertension.*

  c) Rebound hypersecretion of HCl with Ca++ antacids.

- ***Drug interactions of antacids:***

  - *The increase in gastric pH* ***decrease the absorption*** *of acidic drugs as digoxin and iron.*

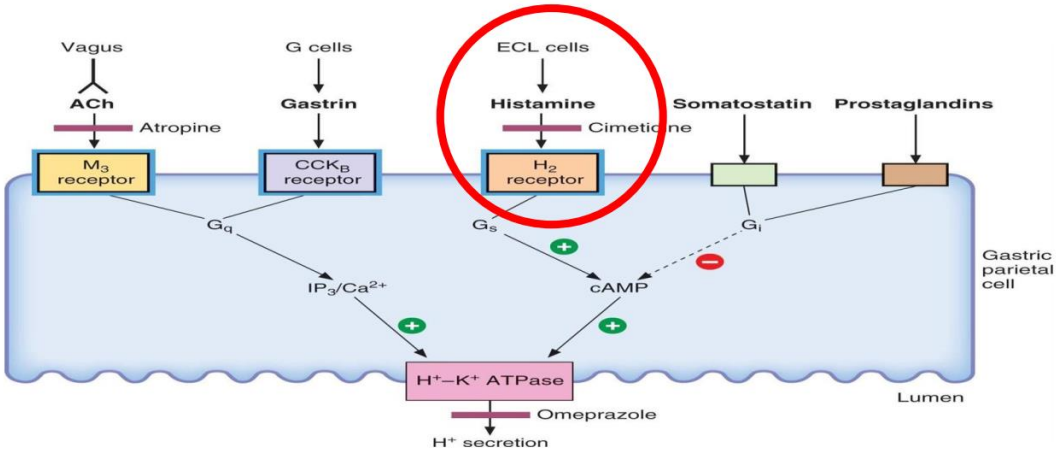
2- Drugs decreasing HCl secretion

A. Selective M1 blockers

Example	• *Pirenzepine - Telenzepine*
MOA	• *Selectively block gastric* ***M1 receptors*** *→ ↓ basal HCl secretion.*
Therapeutic uses	• *They have* ***poor efficacy*** *and* ***undesirable side effects.*** • *They are used as adjuvant therapy with H2 blockers.*
Side effects:	• *High doses produce* ***atropine-like effects****: dry mouth, blurred vision, tachycardia, urine retention.*

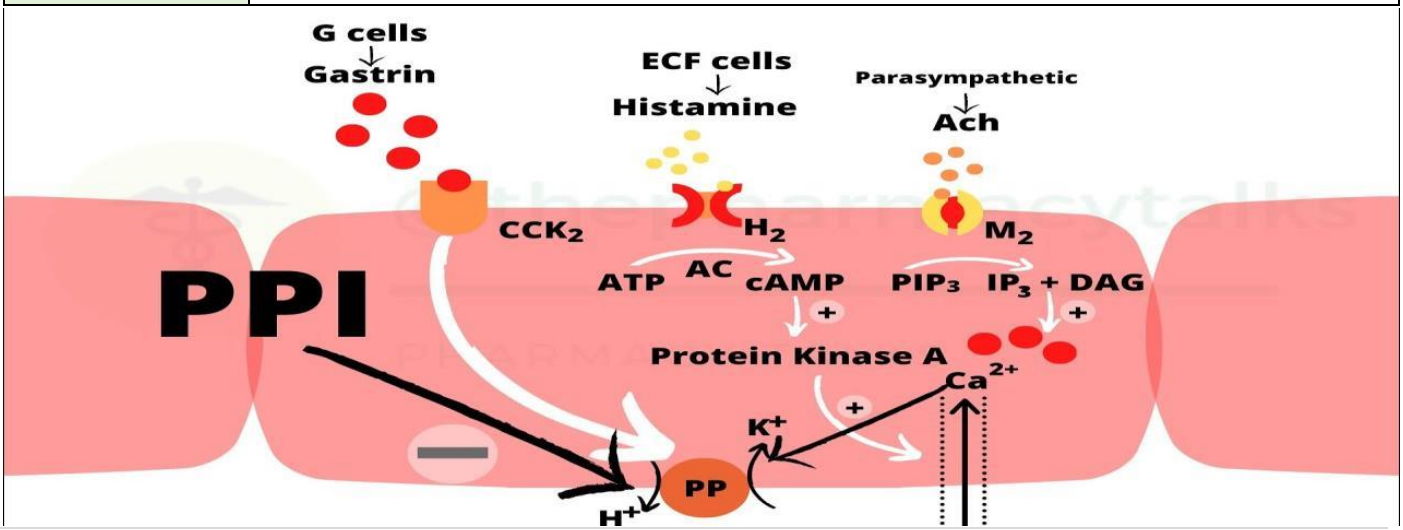
B. H2 blockers

Example	• *Cimetidine – Ranitidine – Famotidine*
MOA	• *Competitive inhibitors of **H2-receptors** on parietal cell with a marked ↓ in **histamine-stimulated HCl secretion.***
Therapeutic uses	*- Duodenal and gastric **ulcers.*** *- Prophylaxis & treatment of **stress ulcers** (after burn or major trauma).* *- **GERD.***
Side effects:	***1) Cimetidine has anti-androgenic effects** (due to block of androgen receptors) leading to ↓ sperm count, impotence & gynecomastia.* ***2) Cimetidine inhibits hepatic microsomal enzymes** (P450) leading to ↓ metabolism of other drugs e.g. theophylline, warfarin etc* ***3) Reversible hepatotoxicity and Reversible anemia.*** ***4) CNS symptoms:** headache, slurred speech, delirium, coma occurs mainly in elderly people with IV administration.*
Precautions of H2 blockers	• *Avoid **sudden withdrawal** to prevent rebound ulceration.* • *Avoid **combination** of cimetidine with drugs having narrow therapeutic index (because cimetidine inhibits microsomal P450 and ↑ their toxicity).*



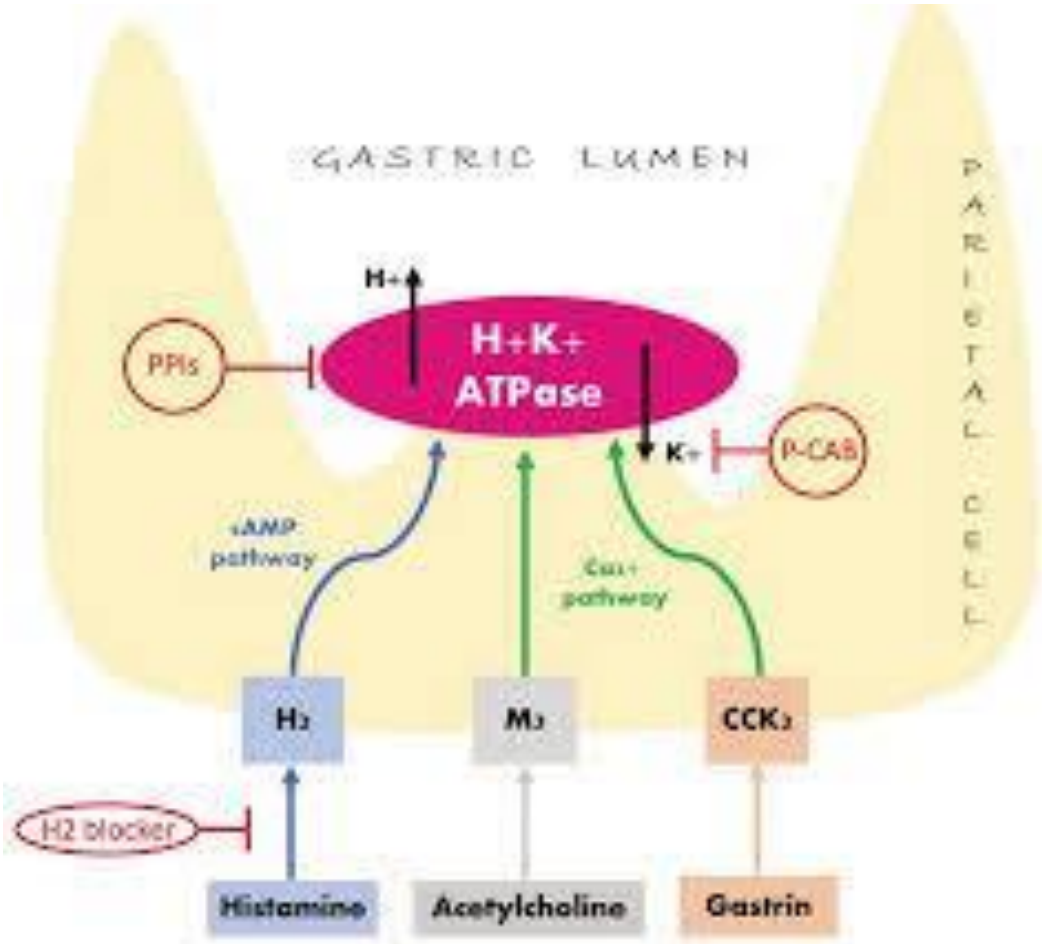
C- Proton pump inhibitors (PPIs):

Example	• *Omeprazole – Lansoprazole – Pantoprazole*
MOA	• ***Irreversible inhibition*** *of gastric H+/K+ ATPase enzyme leading to ↓ both basal & stimulated HCl secretion to the zero level for* ***1-2 days.*** • *Full restoration of acid secretion after stopping the PPI takes about* ***3-5 days*** *(time of re-synthesis of H+/K+ ATPase).* • *Their* ***bioavailability is decreased*** *significantly by food and, ideally, should be administered 1 hour* ***before a meal.***
Therapeutic uses	• ***The same as*** *H2 blockers*
Side effects:	*1) Diarrhea, abdominal colic, dizziness* *2) Decrease* ***vit B12 absorption*** *after more than 12 weeks of therapy due to interference with intrinsic factor secretion by the stomach.* *3) Inhibition of gastric secretion leading to alteration of* ***bioavilability*** *of some drugs, e.g. ketoconazole, digoxin & iron.* *4) Omeprazole selectively* ***inhibits hepatic P450*** *and decreases the elimination of phenytoin, diazepam, warfarin.* *5) Osteoporosis*



D- Potassium Competitive Acid Blockers (P-CABs):

Example	• ***Vonoprazan***
MOA	• *These novel antisecretory drugs differ from PPIs because they compete with K+ and induce a **selective and reversible** inhibition of the proton pump in a dose-dependent manner.*

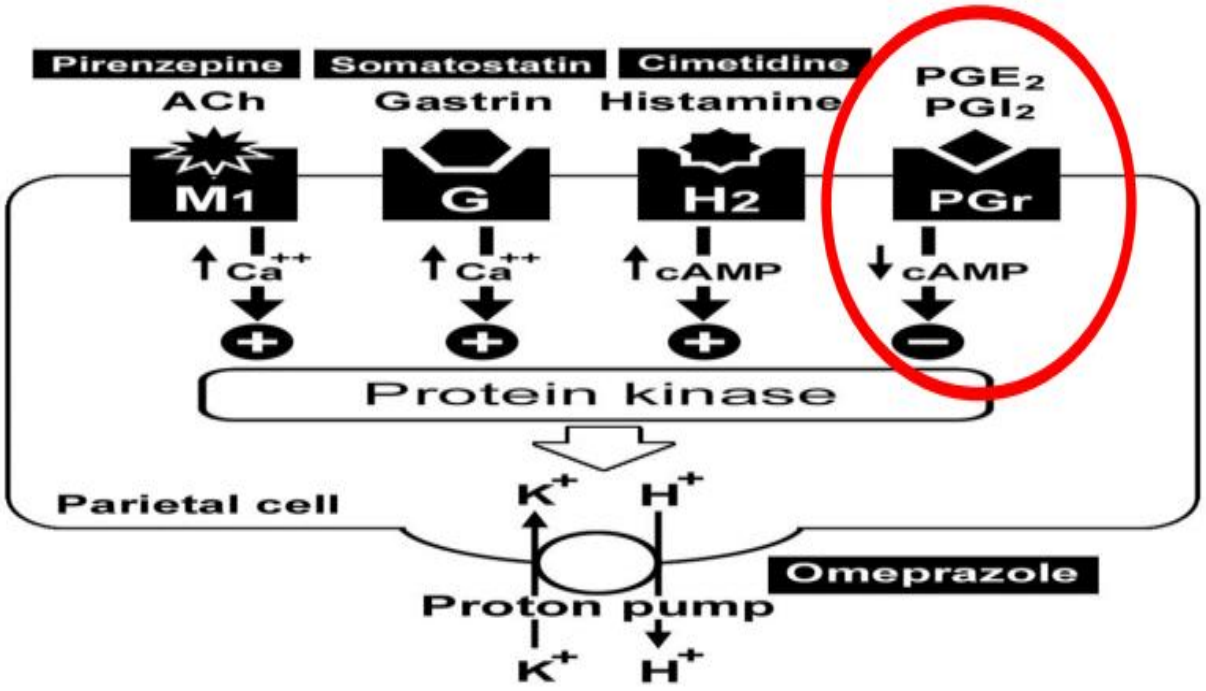


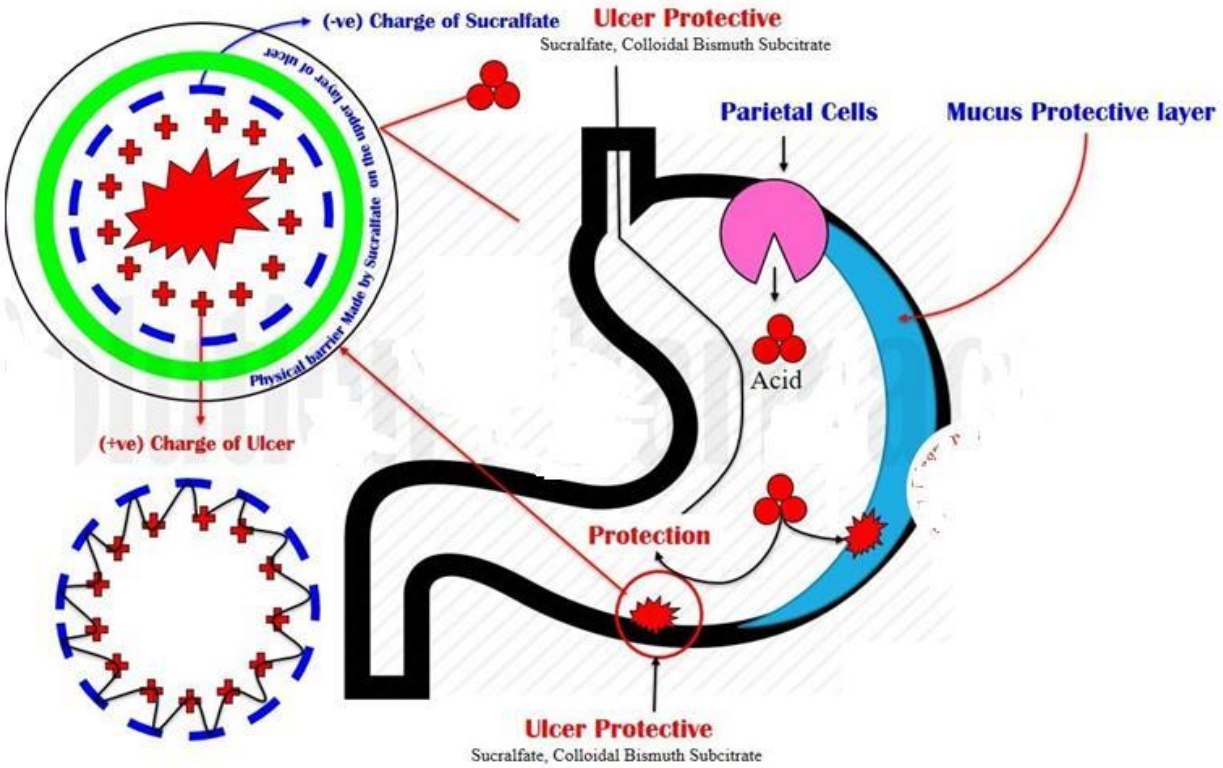
3-Drugs enhancing mucosal defense mechanisms

	Sucralfate	Bismuth compounds	Carbenoxolone	Synthetic PGE1 analogue
Example	•	• *Bismuth subsalicylate*	• *Liquorice derivative having steroid structure.*	• *Misoprostol*
MOA:	• *Needs **acidic medium** to be activated (not with antacids, H2bl, PPIs).* • *The aluminum is released so that the compound develops a strong negative charge and **binds to** the positively charged protein molecules that transude from damaged mucosa.* • *The result is **a viscous paste** that adheres selectively and protectively to the ulcer base.* • *It also inactivates **pepsin and bile acids** and ↑ secretion of **PGs***	• ***As sucralfate** + It has additional antimicrobial activity against **H. pylori.*** • *Both sucralfate and colloidal bismuth compound are **not given simultaneously** with antacids or H2 blockers (at least 30 min must be elapsed in between).*	• *It ↑ production and viscosity of **gastric mucus** and ↑ mucosal resistance.* • *It ↓ pepsin secretion and ↑ secretion of endogenous PGs.*	• *It acts on specific receptors on gastric parietal cells leading to ↓ **histamine - stimulated HCl secretion.*** • *↑ **Mucus and bicarbonate secretion** (cytoprotective action).* • *↑ **Mucosal blood flow** and stimulates mucosal cellular regeneration.*
Side Effects:	• *Constipation (due to presence of aluminum).*	• *Stool & teeth discoloration.* • *Encephalopathy in presence of renal failure*	• ***Salt & water retention** (aldosterone-like effects) → edema & hypertension **especially in** cardiac & renal patients.*	• ***Diarrhea and cramping pain:** due to ↑ GIT motility and water secretion.* • ***Uterine contractions during pregnancy** → abortion.*
C/I	•	•	• *Hypertension & renal failure.*	• *Pregnancy.*

NB:

- ***Synthetic PGE1 analogue (Misoprostol)*** *is used in Prevention of peptic ulcer in high-risk patients e.g. those on long term use of* ***NSAIDs*** *for chronic inflammatory diseases.*





4- Eradication therapy for H. pylori

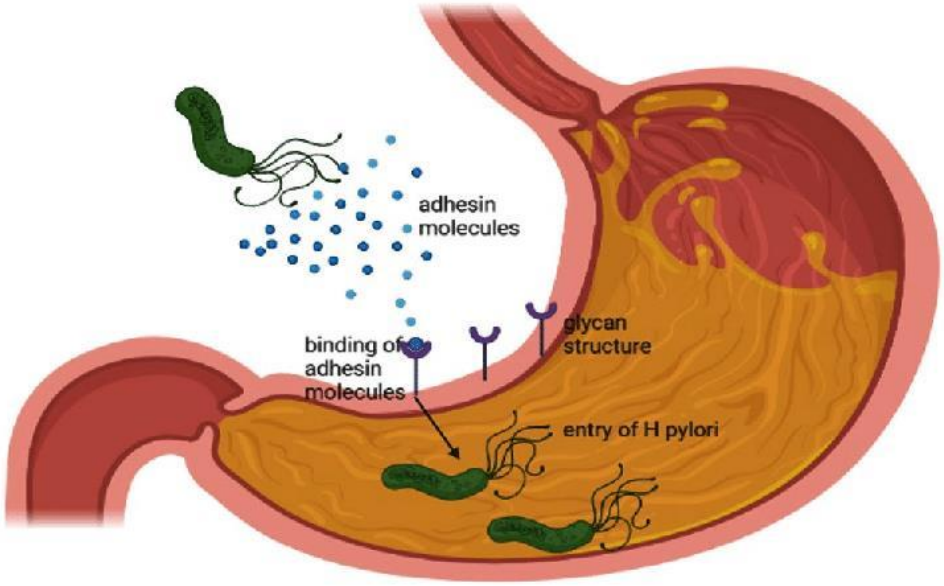
- *Infection with H. pylori is a main cause of* ***recurrence of PU.***
- ***Single antimicrobial agents*** *is usually* ***not effective*** *in eradicating H. pylori due to drug resistance*
- ***<u>The following 10 days "sequential protocol" is highly effective for eradication of H. pylori:</u>***

PPIs
Amoxicillin 1 g
twice daily for 5 days (days 1-5).

PPIs
Clarithromycin 500 mg
Tinidazole 500 mg
twice daily for 5 days (days 6-10).

- ***<u>Current regimens for H. pylori:</u>***

The "classic" triple therapy:	• ***1 or 2 weeks*** • *Omeprazole, Clarithromycin, and Amoxicillin or Metronidazole.*
Quadruple therapy:	• *Omeprazole, two Antibiotics and Bismuth.*



NB:

- *H. pylori* ***develop resistance*** *to metronidazole and clarithromycin,* ***but resistance is uncommon*** *to tetracycline and amoxicillin.*

- ***PPIs or H 2 blockers*** *are often included to provide symptomatic relief, promote ulcer healing, and increase the sensitivity of the organism to antimicrobial agents (concentrate it).*