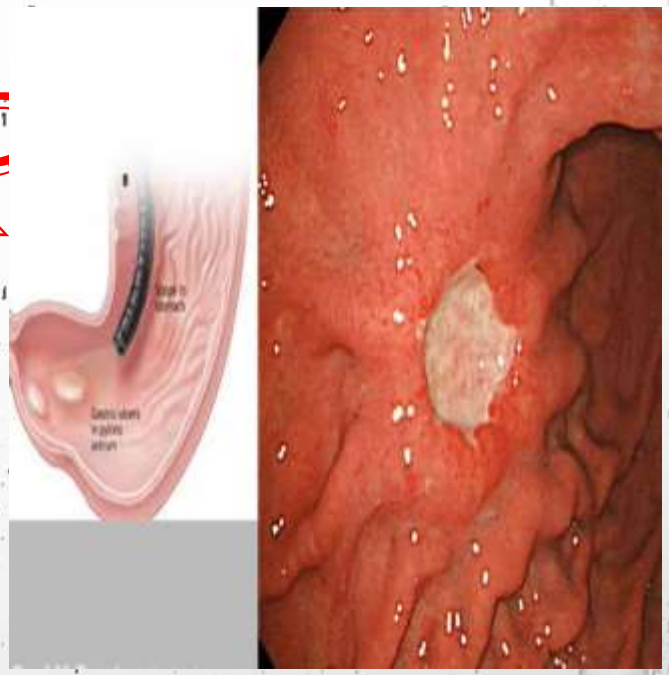
PEPTIC ULCER



Dr/ Heba Ahmed Hassan

Assistant professor of clinical pharmacology, faculty of medicine, MUTAH university

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PEPTIC ULCER DISEASE (PUD)

LOCATION

Gastric Ulcer (Stomach)

Duodenal Ulcer (Duodenum)

CAUSES

H. pylori Infection

NSAIDs (e.g. Ibuprofen, Aspirin)

Acid Damage (HCl)

PATHOPHYSIOLOGY

Normal:

Mucus Barrier

In PUD: ↓ Mucus / ↑ Acid

SYMPTOMS

- Burning Pain
- Bloating & Nausea
- Loss of Appetite

Severe : Bleeding
(Vomiting Blood / Black Stool)

Damage to Lining

ULCER
(Open Sore)

TREATMENT

Antibiotics
(Kill H. pylori)

PPIs (↓ Acid)
e.g. Omeprazole

Antacids
(Neutralize Acid)

COMPLICATIONS

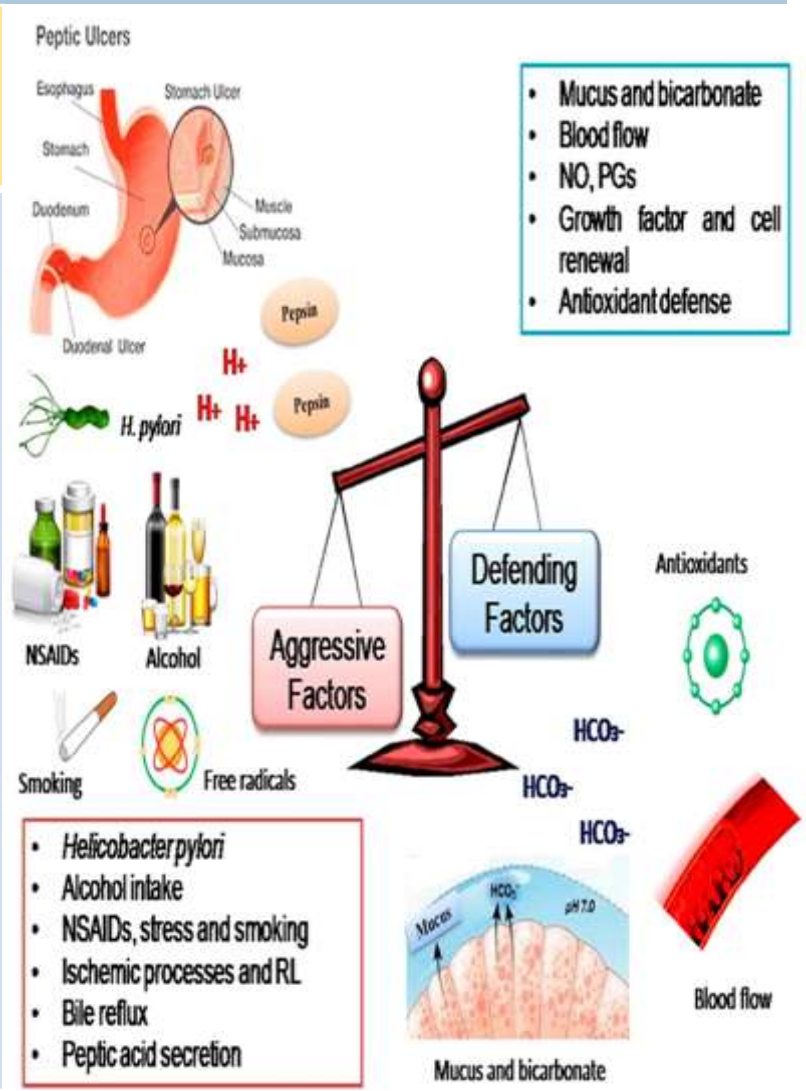
Bleeding → Perforation → Obstruction

H. pylori / NSAIDs → ACID DAMAGE → ULCER FORMATION → PAIN & COMPLICATIONS

• PATHOGENESIS

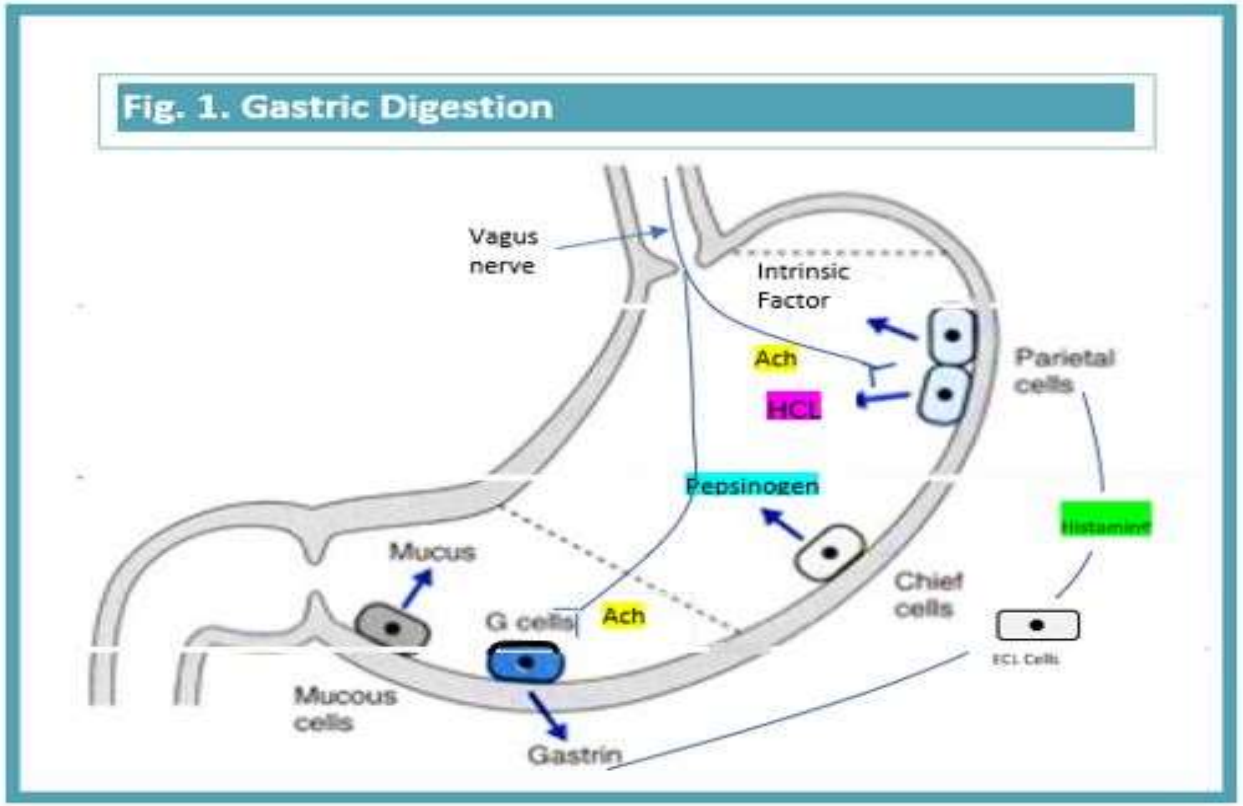
• Unbalancing between aggressive factors & defensive factors.

• A. Aggressive factors:	• B. Defensive factors:
• Gastric acid secretion. • Pepsin. • Bile. • Helicobacter pylori.	1.Mucus & bicarbonate secretion 2.Thick lipoprotein coat. 3.Tight intercellular junctions. 4.Processes of restitution and regeneration after cellular injury. 5.Gastric mucosal blood flow.



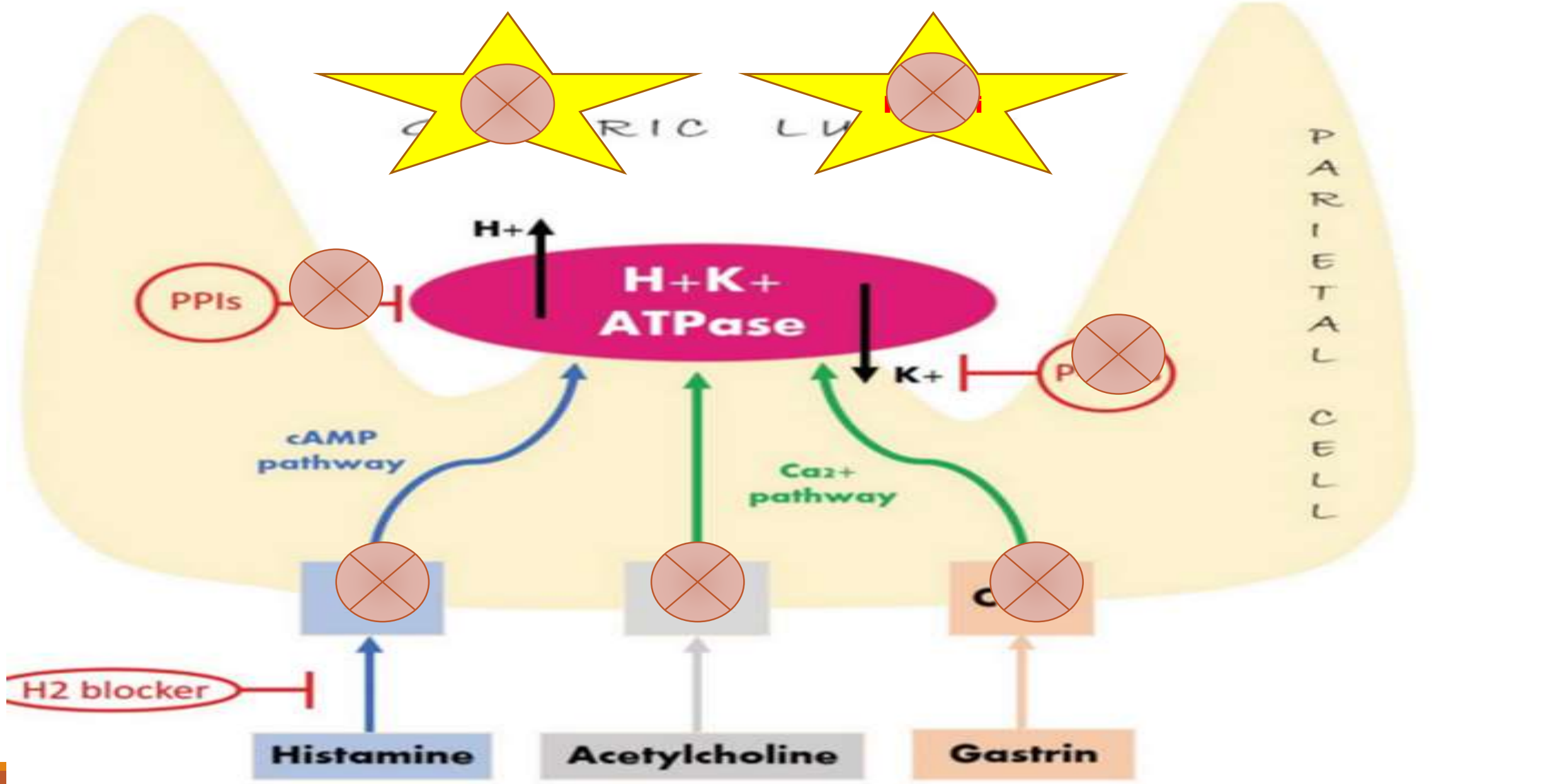
SECRETION OF HCL

- Nocturnal acid secretion (which depends largely on histamine)
- Meal-stimulated acid secretion (which is stimulated by gastrin, Ach and histamine).



Helicobacter pylori

- H. pylori is a spiral-shaped bacterium that is found in the gastric mucus layer or adherent to the epithelial lining of the stomach.
- 50% of the world population is infected. It causes: duodenal/gastric ulcers and gastric cancer.
- H pylori causes more than 90% of duodenal ulcers and more than 60% of gastric ulcers

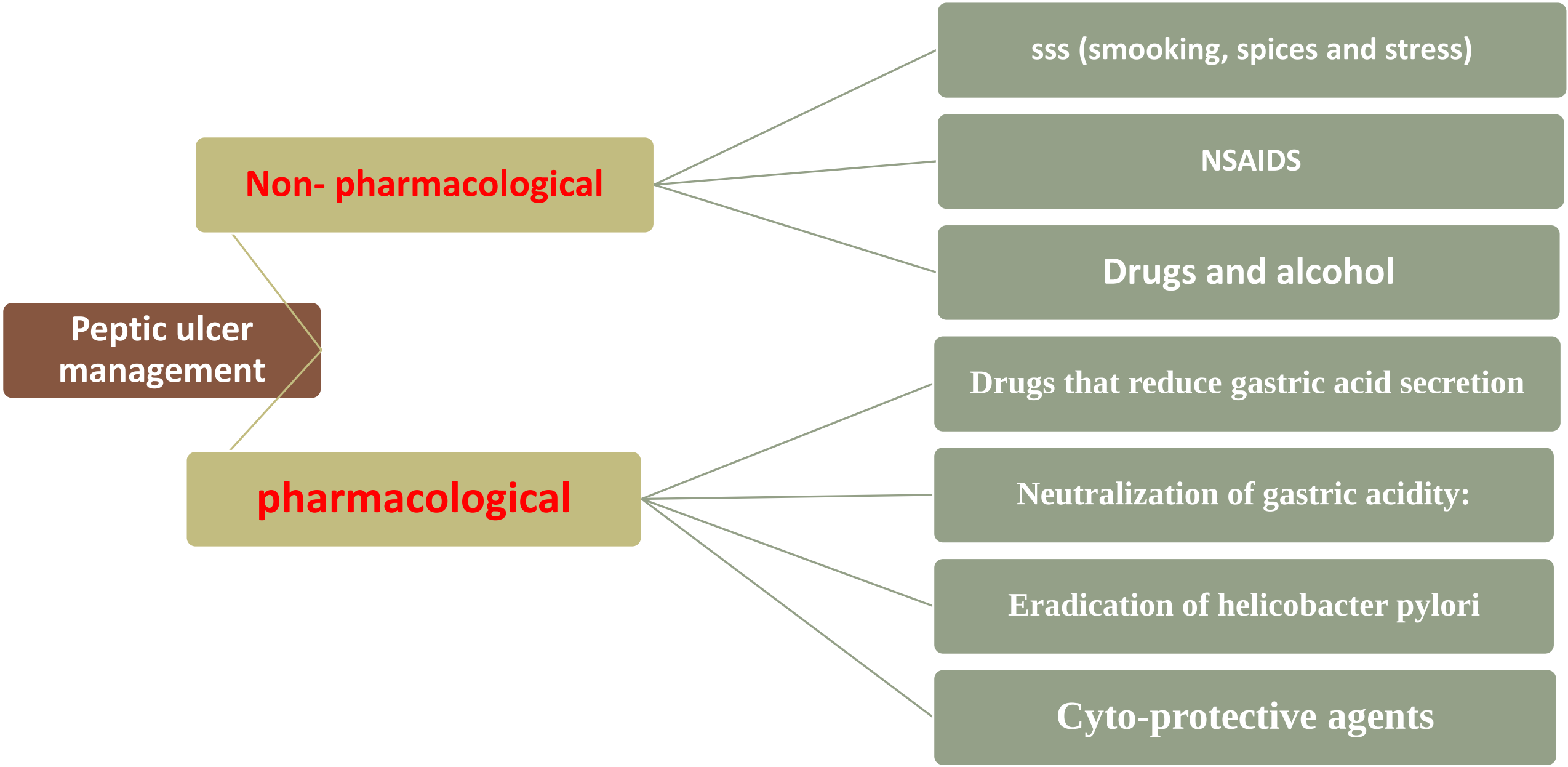

PARIETAL CELL
H+
H+K+ ATPase
K+
PPIs
cAMP pathway
Ca2+ pathway
H2 blocker
Histamine
Acetylcholine
Gastrin

SYMPTOMS: Pain (duodenal ulcer) and vomiting (gastric ulcer)

COMPLICATIONS: hemorrhage, perforation, cancer

GOAL OF THERAPYS

- Treatment of symptoms.
- Promotion of healing (4-8weeks for D.U. Or 8-16 weeks for G.U).
- Prevention of recurrence [maintenance dose (half the normal dose) for at least 6 months].


Peptic ulcer management
Non- pharmacological
sss (smooking, spices and stress)
NSAIDS
Drugs and alcohol
pharmacological
Drugs that reduce gastric acid secretion
Neutralization of gastric acidity:
Eradication of helicobacter pylori
Cyto-protective agents

1- Drugs that reduce gastric acid secretion

- Proton pump inhibitors. PPIs
- Potassium channel blocker
- H2 histamine receptor antagonists.
- Muscarinic antagonists.
- Gastrin antagonists (proglumide).
- PG analogue.

1. Proton-pump inhibitors

Omeprazole, esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole

PHARMACOKINETICS:

Absorption: Rapidly absorbed.

The bioavailability is decreased approximately 50% by food, hence drugs should be administered on an empty stomach.

Acid inhibition lasts up to 24 hours owing to the irreversible inactivation of the proton pump.

Distribution: Bound to plasma protein (95%).

Metabolism: Hepatic metabolism [CYP3A4 &CYP2C19 (genotype)]. Rapid first-pass & systemic hepatic metabolism.

PPIs are administered as inactive prodrugs. To protect the acid-labile prodrug from rapid destruction within the gastric lumen.

Mechanism of action:

- Protonated within the canaliculus.
- **Irreversibly (covalent bond)** inhibits H+-K+ ATPase (proton pump).At least **18hrs**. Are required for the synthesis of new H+/K+ ATPase pump molecules.

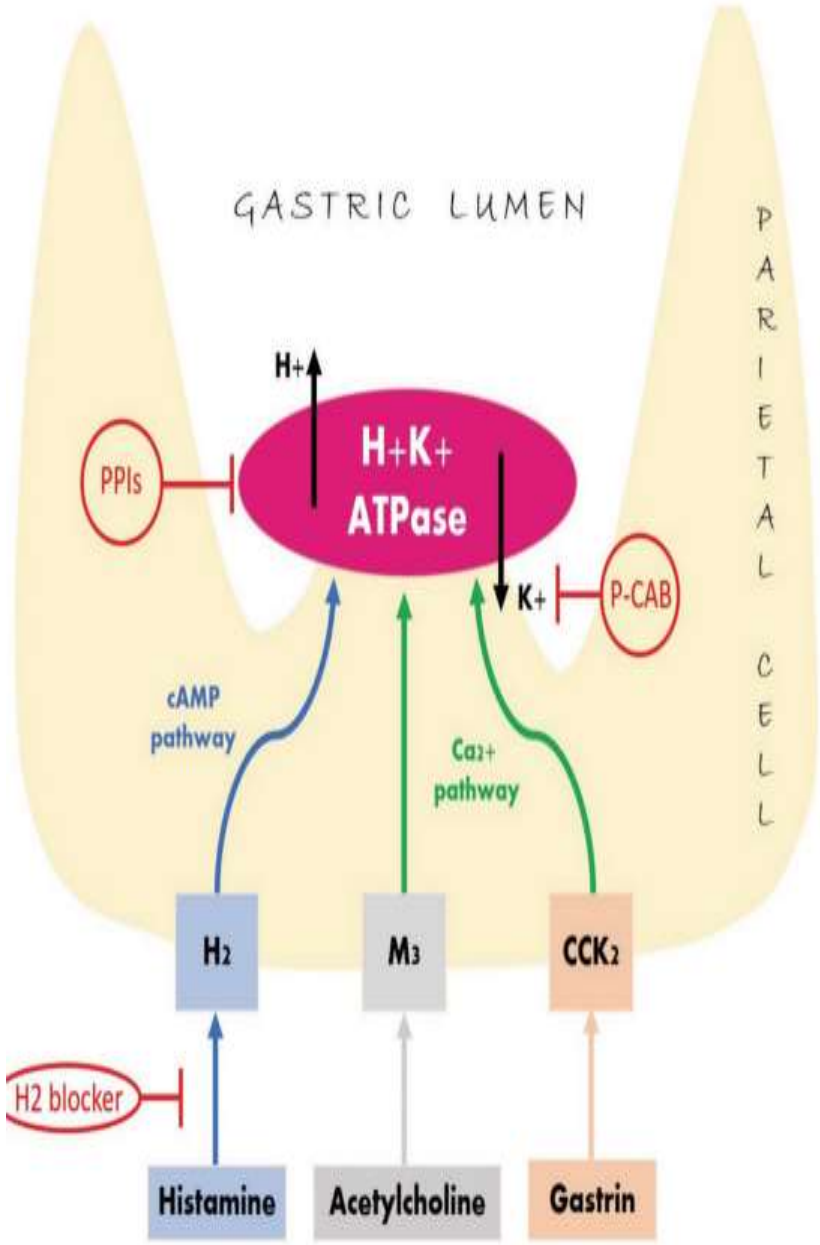
Pharmacological action:

1 inhibit both **fasting & meal-stimulated** gastric acid secretion (more than **95%).**

2 anti-H pylori:

A)direct.

B)↑PH →↓ minimal inhibitory concentrations of antibiotics against HP.



USES

1- gastroesophageal reflux disease (GERD).

2- peptic ulcer

3- Zollinger-Ellison syndrome.

4- Prevention of stress-related mucosal bleeding (due to mucosal ischemia have normal or decreased acid secretion)

Adverse effects: (rare)

1. G.I.T. (Nausea, diarrhea, colic).

2. C.N.S. (Headache, drowsiness, dizziness).

3. Long-term elevation of gastric PH may cause: A- hypergastrinemia→ ECL hyperplasia which leads to: Carcinoid tumors (rats) and Rebound hypersecretion upon discontinuation of the drug.B-bacterial overgrowth in G.I.T. → ↑ Risk of respiratory and enteric infections.

4. Skin rash, subacute myopathy & arthralgias.

5. Chronic treatment decreases absorption of B12.(Acid is important in releasing vitamin B12 from food.

6. Chronic treatment →↑ risk of hip fracture. (Acid also promotes absorption of food-bound minerals (iron, calcium, zinc))

- **N.B. Point 5&6 called nutritional adverse effect**

Drug interactions

Because of the short half-lives of PPIs, clinically significant drug interactions are **rare.**

- Enzyme **inhibition**: omeprazole may inhibit CYP2C19 (e.g., warfarin, phenytoin, and diazepam).
- Enzyme **enhancer** Lansoprazole may increase theophylline clearance.
- Rabeprazole and pantoprazole have no significant drug interactions.

↓ Gastric acidity may alter the absorption of drugs for which intragastric acidi affects drug bioavailability, e.g,. Ketoconazole, ampicillin ester, iron salts & digoxin.

2. Potassium-Competitive Acid Blockers (P-CABs)

Vonoprazan, Tegoprazan, Keverprazan

These are the latest major advancements beyond proton pump inhibitors (PPIs).

Mechanism:

Reversible **(non- covalent bond)** inhibition H^+/K^+ ATPase (proton pump).

Compete with potassium (K^+) → rapid, strong and reversible acid suppression

Advantages over PPIs:

Faster onset of action, active drug, not affected by food or media

Stronger acid suppression

Not affected by CYP2C19

Metabolism: No need for activation in an acidic environment

uses:

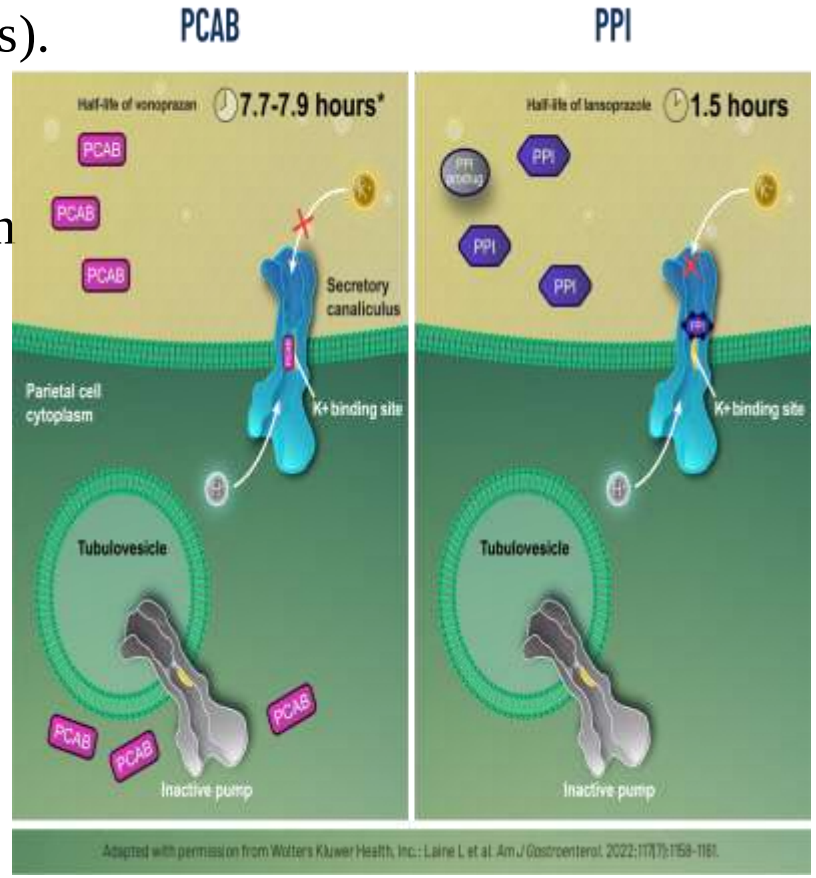
Peptic ulcer disease

GERD

NSAID-induced ulcers

Helicobacter pylori eradication

Studies show P-CABs are superior to PPIs in ulcer healing and H. pylori therapy



3. H2 histamine receptor antagonists

Cimetidine, Ranitidine, Famotidine, Nizatidine

Pharmacokinetics

➢**Absorption:** Rapidly absorbed.

➢**Distribution:** Crosses the placenta. Therefore, they should not be administered to pregnant women (CLASS-B).
Secreted in breast milk.

➢**Metabolism:** Cimetidine, ranitidine & famotidine undergo first-pass hepatic metabolism, resulting in a bioavailability of approximately 50%

Nizatidine has little first-pass metabolism and a bioavailability of almost 100%

➢ **Elimination:** H2 antagonists are cleared by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion (large part excreted by urine).

Pharmacodynamics:

- **Competitively** inhibit the interaction of **histamine with H2 receptors**.
- ↓ Gastric acid secretion.
- H2 antagonists are especially effective at inhibiting nocturnal acid secretion (which depends largely on histamine) but have a modest impact on meal-stimulated acid secretion (which is stimulated by gastrin and acetylcholine as well as histamine). Thus they block more than 90% of nocturnal acid but only 60-80% of day time acid secretion.

Uses:

1. Peptic ulcer.
2. Zollinger-ellison syndrome.
3. Gastro-esophageal reflux disease (GERD).
4. Other conditions (stress ulcer, Preanesthetic medication “emergency”).

Adverse effects

- Diarrhea, headache, fatigue, nausea, myalgia, constipation (common).
- Mental status changes (confusion, hallucination, agitation), commonly with Cimetidine (I.V., Elderly, renal or hepatic dysfunction). Blocks **H_2 receptors in the brain**
- Gynecomastia or impotence in men & galactorrhea in women (anti-androgen, ↑prolactin & estradiol), specific to Cimetidine
- Cimetidine inhibits cytochrome P450 hepatic enzymes, which affects many drugs related to hepatic metabolism
- Rapid I.V. Infusion → bradycardia & hypotension through blockade of cardiac H2 receptors.
- 4. thrombocytopenia
- 5. **Reversible** abnormalities in liver chemistry.

4. selective muscarinic antagonists (M1)

pirenzepine telenzepine

- ↓ Basal secretion (40- 50%).
- ↑ Gastric mucosal blood flow (M2 presynaptic on adrenergic fibers → ↓ Ne).
- ↑ Motility → ↑ LESP "lower esophageal sphincter pressure" (M1 receptors have a role in inhibitory motility pathway).

5. prostaglandin analogue, misoprostol (cytotec)

A methyl analog of PGE1.

Mechanism of action & pharmacodynamics:

Both acid inhibition & mucosal protection:

- Inhibits acid secretion (inhibits adenyl cyclase & gastrin release).
- Stimulates mucus and bicarbonate secretion.(MAIN)
- Increases blood flow.

2. Other actions:

- Stimulates intestinal electrolyte & fluid secretion.
- Stimulates intestinal motility.
- Stimulates uterine contraction.

Uses:

Prevention of NSAID-induced ulcers in high-risk patients.

Side effects:

1. Diarrhea & abdominal pain (10-20%).
2. Uterine contraction (abortion & vaginal bleeding).

2- Neutralization of HCL (ANTIACID)

SYMPTOMATIC TREATMENT

Chemical

Physical

Adsorb (HCL; pepsin) and Demulcent

1- Al^{+3}hydroxide gel. 2- Mg^{+2}trisilicate.

Systemic

- Na^{+}bicarbonate

Local (Non-systemic)

1 Mg^{+2}salts (Hydroxide &Trisilicate).

2 Al^{+3}salts (Hydroxide & Phosphate gel).

3 Ca^{+2}salts (Carbonate).

Pharmacological actions:

❑Antipeptic effects:

I. Reduction of gastric acidity will suppress the activity of pepsin: Activity decreases as PH increases above 2 and is irreversibly inactivated at PH 7

II. Al+3 containing antacids → adsorb pepsin.

❑ Effect on acid secretion:

↑ PH (in gastric antrum) → ↑ gastrin → rebound acid secretion.

❑ Gastrointestinal motor activity:

- Al+3 → relax smooth muscle of stomach (astringent) → constipation.
- Mg+2 → ↑ cholecystokinin → ↑motor activity.
- Mg+2 → osmotic laxative effect.

❑ Side effects:

- Change bowel habits
- Rebound hyperacidity
- Decrease absorption of some drugs
- Cation overdose (sodium and calcium)

Magalderate [rioper]

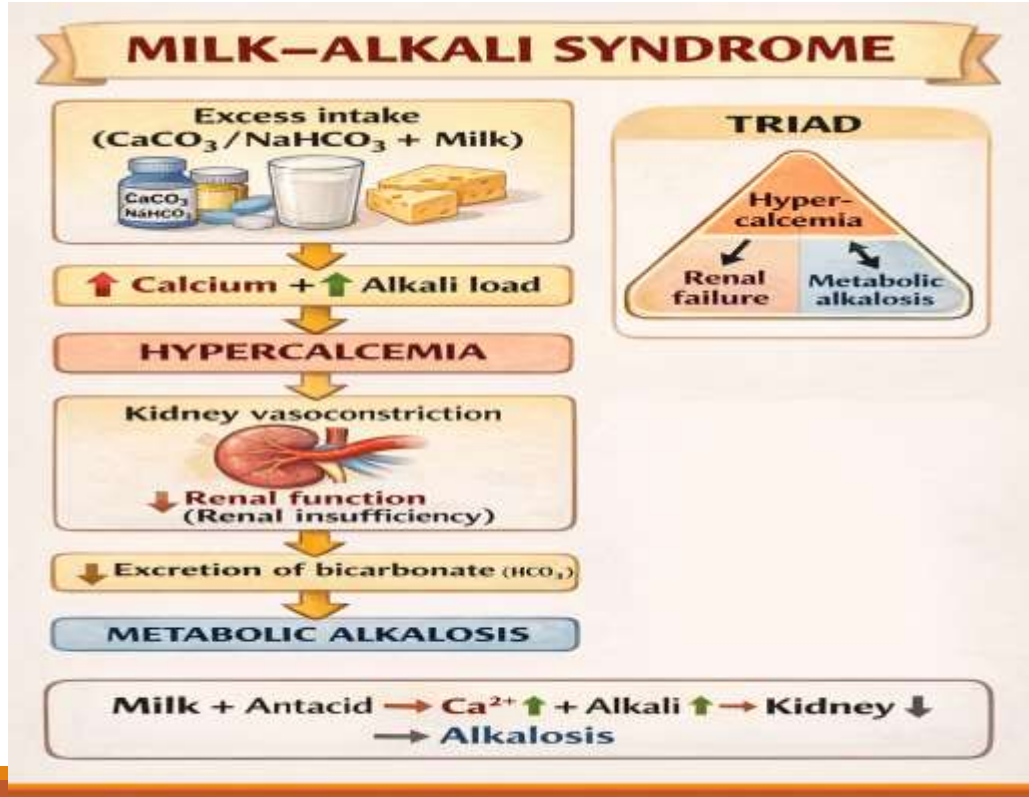
(AL hydroxide + magnesium hydroxide)

- Both magnesium and aluminum are absorbed and excreted by the kidneys. Hence, patients with renal insufficiency should not take these agents for long-term therapy.

N.B.

(milk-alkali syndrome)

Excessive doses of either sodium bicarbonate or calcium carbonate with calcium-containing dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis.



3- ERADICATION OF HELICOBACTER PYLORI
For two weeks.

B	· **Bismuth subcitrate** (120mg four times daily). · **Bismuth subsalicylate** (2 tablets; 262 mg each).
M	· **Metronidazole** (250 mg three times daily) · Tinidazole (500mg bid)
A	· Amoxicillin (500mg three times daily). · **Tetracycline** (500 mg four times daily).

Peptic ulcer & helicobacter pylori

❖ **These regimens are used for 10-14 days, then PPIs should be continued once daily for 4-6 weeks.**

Quadruple (1ST LINE)	**Bismuth + Metronidazole+ Tetracycline+ PPI**
Triple	▪ **PPI + Amoxicillin + Rifabutin** ☞ **Useful when resistance suspected** ▪ **Vonoprazan + Amoxicillin + Clarithromycin** ☞ **Useful when clarithromycin sensitive**
Dual	· **Amoxicillin + Omeprazole** · **Vonoprazan + Amoxicillin**

4-MUCOSAL PROTECTIVE AGENTS

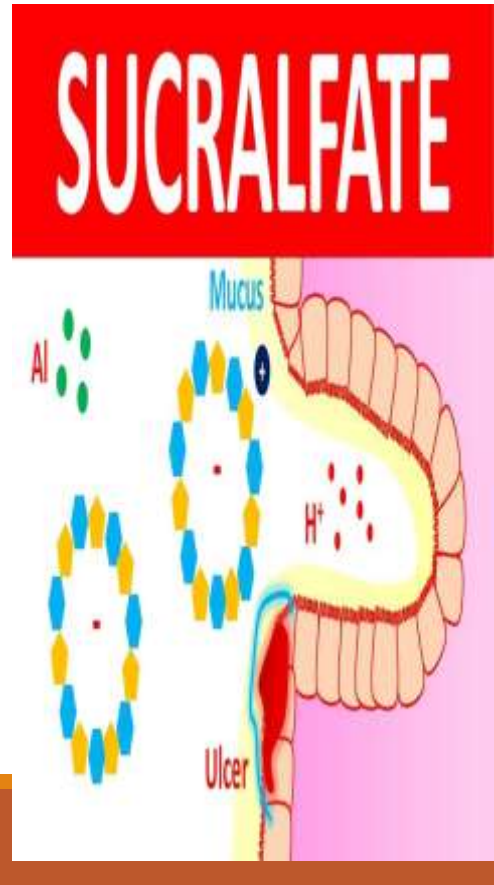
A- Sucralfate: (sucrose octasulfate + Al+3 hydroxide)

Mechanism of action:

1.At acid PH (below 4) → polymerization → gel → selective binding to necrotic ulcer tissues for up to 6 hrs. Sucrose sulfate (negatively charged) binds to proteins (positively charged) in the base of ulcers or erosion, forming a physical barrier.

2.Absorbs bile salts & pepsin.

3.Stimulates PG & bicarbonate secretion



Side effects:

1-Constipation.

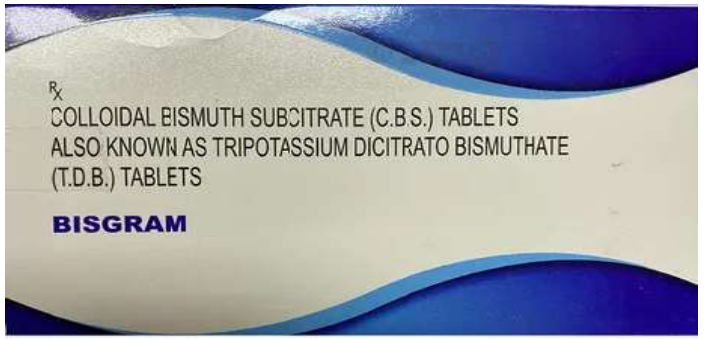
2-dry mouth.

3- 3% absorbed. Not be used for long period in patients with renal insufficiency.

4- adsorb [tetracycline, phenytoin , digoxin , cimetidine]

B- BISMUTH COMPOUND: COLLOIDAL BISMUTH SUBCITRATE (DENOL):

Mechanism of action: (needs acid PH for activation).



1) Coats ulcer.
2) Stimulate the production of mucus and bicarbonates
3) Lysis of Helicobacter pylori.
4) Decreasing stool frequency and fluidity are used in diarrhea of acute infections(travelers' diarrhea)

Side effects

1) Black color (oral cavity & stool). Blackening of stool may be confused with G.I.T. Bleeding.
2) Prolonged use → encephalopathy (ataxia, headaches, confusion, seizures). Thus, it should be used for a short period only & avoid in renal impairment.

N.B.

Bismuth compound & Sucralfate should not be administered simultaneously with antacids or H2 antagonists.

C- Rebamipide

PK

Absorption: It is a highly lipophilic, poorly water-soluble

Distribution: It has a high affinity for blood proteins

Rebamipide also accumulates in the reproductive organs

Preclinical studies showed that rebamipide is found in breast milk.

Metabolism: Rebamipide undergoes minimal first-pass metabolism. It is metabolized by the enzyme CYP3A4.

Elimination: 10% of the administered dose is eliminated in urine, and the remainder is eliminated as inactive metabolites in feces

mechanism of action:

- ↑ Prostaglandin synthesis (PGE2, PGI2)
- ↑ Mucus secretion + ↑ Bicarbonate
- ↑ Mucosal blood flow

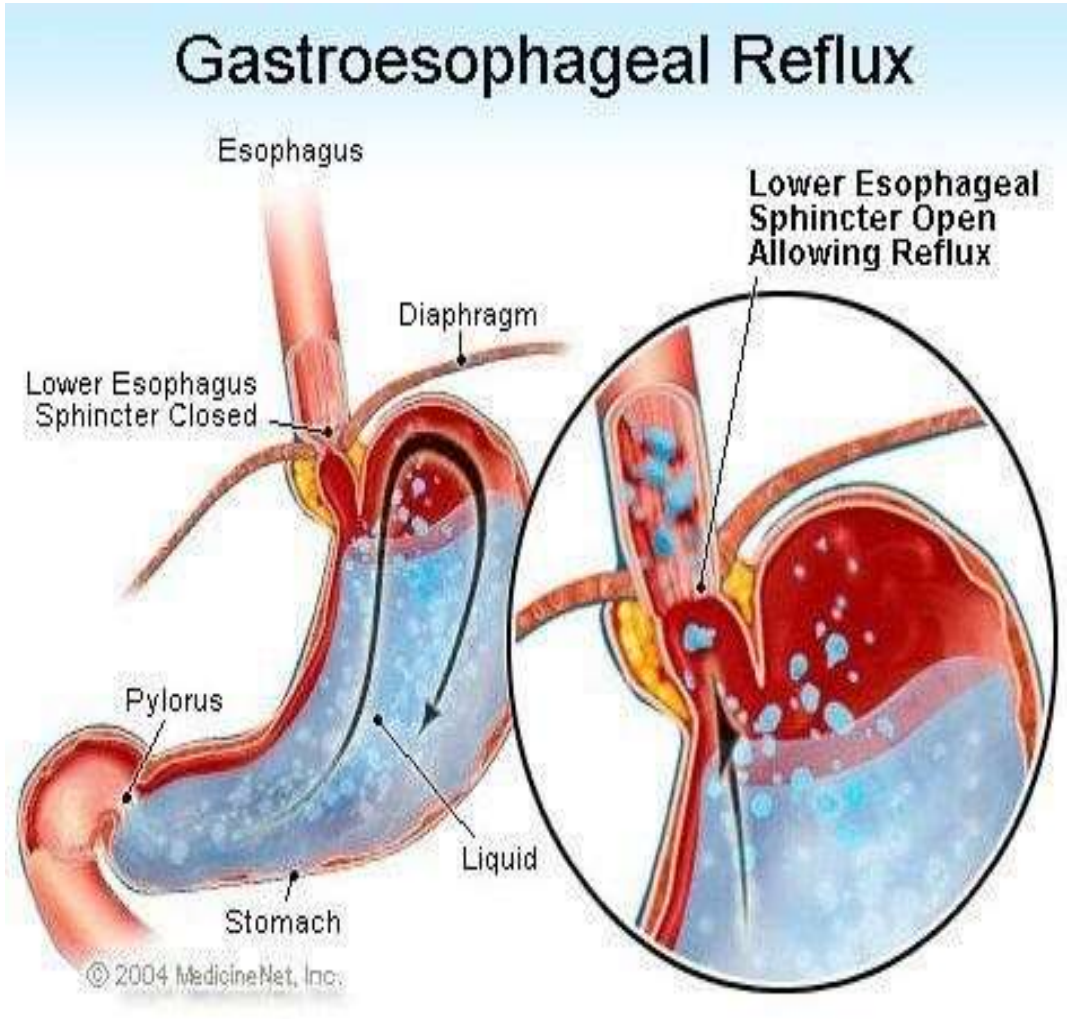
Indications: Peptic ulcer disease, Gastritis, Adjunct in GERD

adverse effects: generally well tolerated: Nausea, Constipation, Headache

GASTRO-ESOPHAGEAL REFLUX DISEASE (GERD)

GERD is a chronic condition where stomach acid flows backward into the esophagus. This causes common symptoms like heartburn and regurgitation. Over time, GERD may result in:

- Erosive esophagitis
- Peptic stricture (esophageal narrowing)
- Barrett's esophagus (BE) – a precancerous change in the esophagus lining
- Esophageal adenocarcinoma (a type of cancer)



pharmacolgical management according to severity of GERD:

Stage I (mild)	**Sporadic uncomplicated heart burn, less than 2-3 episodes/week. Treated with:** **· Life style modification, including diet, weight loss, etc.** **· Antacids and/or H_2-receptor antagonists as needed.**
Stage II (moderate)	**Frequent symptoms more than 2-3 episodes/week (with or without esophagitis).** H_2 receptor blockers but ppi preferred
Stage III (sever)	**Chronic, unrelieved symptoms or immediate relapse after stopping therapy.** **· PPIs either once or twice daily**

GERD & pregnancy:

Mild cases: conservatively, antacids or sucralfate. (safest)
If symptoms persist: H2 receptor antagonists (ranitidine).
Intractable symptoms or complicated reflux disease: lansoprazole.

GERD& children:

Omeprazole is safe and effective for treatment of erosive esophagitis & GERD.

● Role of prokinetics in the treatment of GERD

- Increase LES pressure, enhance esophageal clearance, speed up gastric emptying

☞ Overall → reduce reflux episodes

- But the most effective therapy for GERD still is suppression of acid production by the stomach.

Metoclopramide & domperidone:

- used in the treatment of symptomatic GERD but are not effective in patients with erosive esophagitis.
- it is used mainly in combination with anti-secretory agents.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