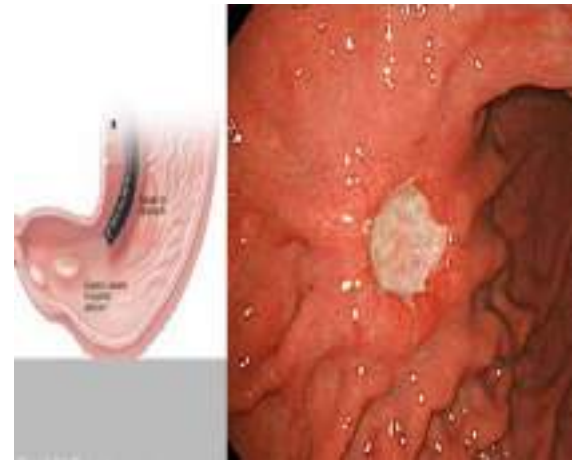
Peptic ulcer and GERD treatment



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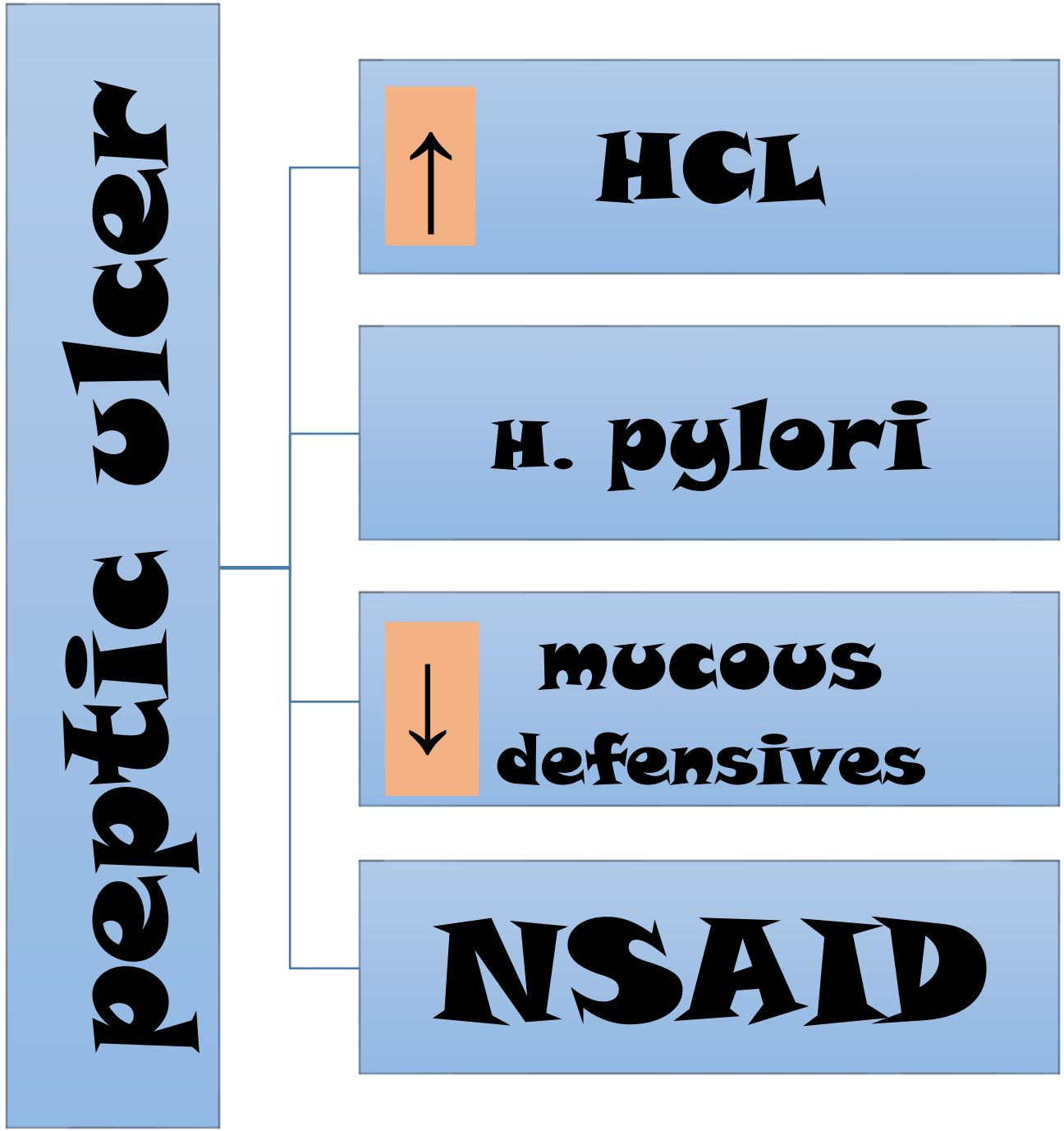
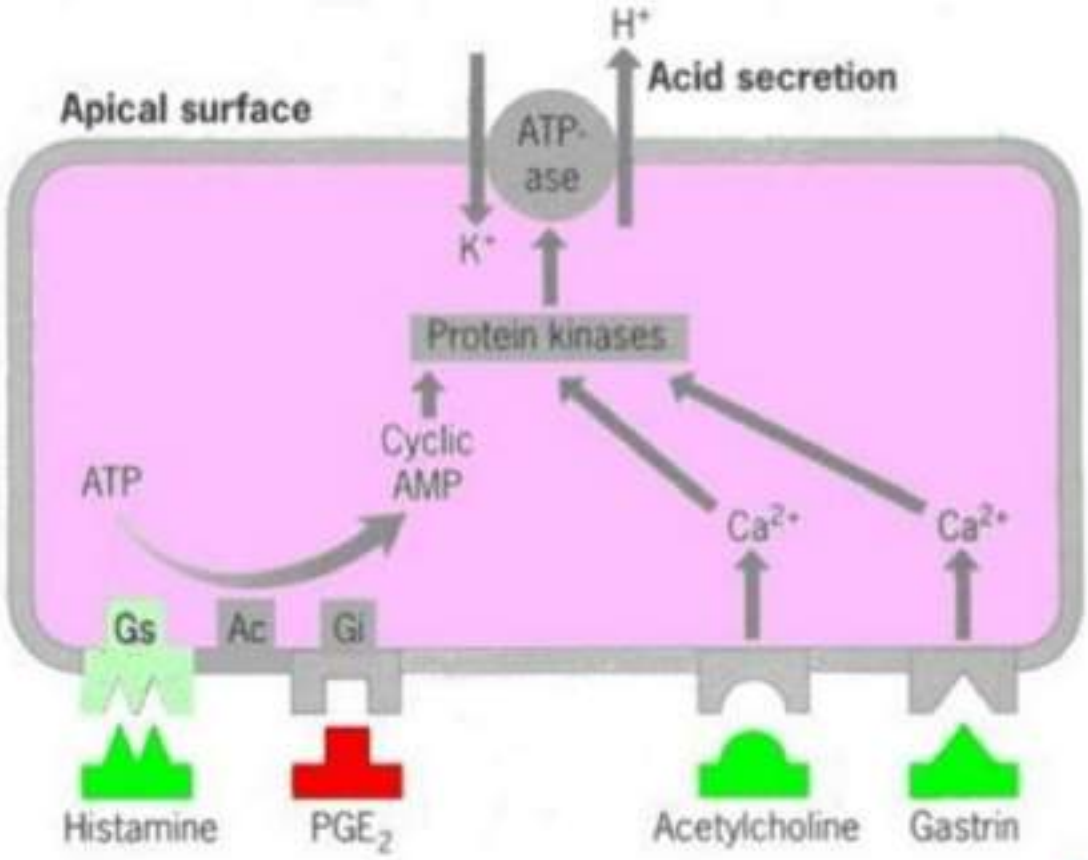
PATHOGENESIS :Unbalancing between

• 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.


peptic ulcer
↑
HCL
H. pylori
↓
mucous defensives
NSAID

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 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.

Clinical pictures

Symptoms:

- **Pain (duodenal ulcer).**
- **Vomiting (gastric ulcer)**

Complications:

A. Hemorrhage.

B. Perforation

C. cancer (gastric ulcer).

Goals of therapy

- 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].

A –Non-pharmacological treatment

- ❖ SSS (smooking, spices, and stress)
- ❖ NSAIDS
- ❖ Drugs and alcohol

B- TREATMENT OF PEPTIC ULCER

1.drugs that reduce gastric acid secretion:

a. **proton pump inhibitors. PPIs**
b. **H2 histamine receptor antagonists.**
c. **muscarinic antagonists .**
d. **gastrin antagonists (proglumide).**
e. **PG analogue.**

2. Neutralization of gastric acidity:

Antacids.

3. Eradication of Helicobacter pylori

4. Cytoprotective agents

A- sucralfate.

B- colloidal bismuth

C- PG analogues (misoprostol).

D- carbenoxolon

(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 theacid-labilel prodrug from rapid destruction within the gastric lumen.

Mechanism of action

- Protonated within the canaliculus (depending on its Pka).
- **Irreversibly** inhibits H+-K+ ATPase (proton pump).
- At least **18 hours** are required for the synthesis of new H+/K+ ATPase pump molecules.

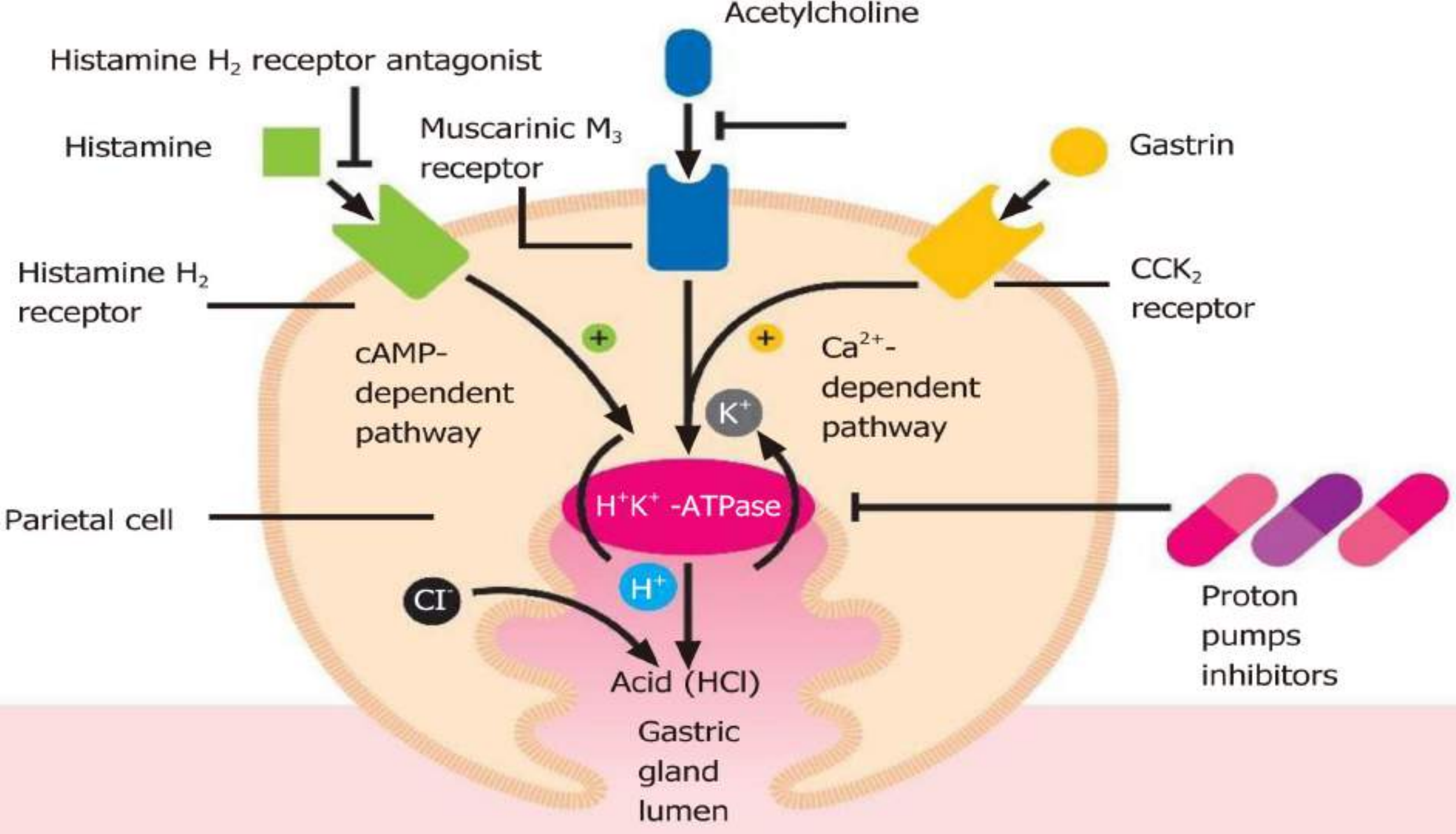
Pharmacological action

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.


Acetylcholine
Histamine H_2 receptor antagonist
Histamine
Muscarinic M_3 receptor
Gastrin
Histamine H_2 receptor
CCK_2 receptor
cAMP-dependent pathway
Ca^{2+}-dependent pathway
K^+
H^+K^+ -ATPase
Parietal cell
H^+
Cl^-
Proton pumps inhibitors
Acid (HCl)
Gastric gland lumen

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).
   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. Points 5&6 called nutritional adverse effects

Drug interactions

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

Enzyme **inhibition**: omeprazole may inhibit CYP2C19 (warfarin, phenytoin, and diazepam).

Enzyme **enhancer** Lansoprazole may enhance clearance of theophylline.

Rabeprazole and pantoprazole have no significant drug interactions.

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

(2) H2 histamine receptor antagonists

Cimetidine Ranitidine Famotidine Nizatidine

Pharmacokinetics

- **Absorption:** Rapidly absorbed.
- **Distribution:** Cross 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).
- Gynecomastia or impotence in men & galactorrhea in women (anti-androgen, ↑prolactin & estradiol).specific to **cimetidine**
- **Cimetidine** inhibits cytochrome P450 hepatic enzymes
- Rapid I.V. Infusion → bradycardia & hypotension through blockade of cardiac H2 receptors.
- 4. thrombocytopenia
- 5. **Reversible** abnormalities in liver chemistry.

(3) 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).

(4) prostaglandin analogue, misoprostol (cytotec)

- **A methyl analog of PGE1.**

Mechanism of action & pharmacodynamics:

1.Both acid inhibition & mucosal protection:

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

- 2.Other actions:
- Stimulates intestinal electrolyte & fluid secretion.
- Stimulates intestinal motility.

Stimulates uterine contraction.

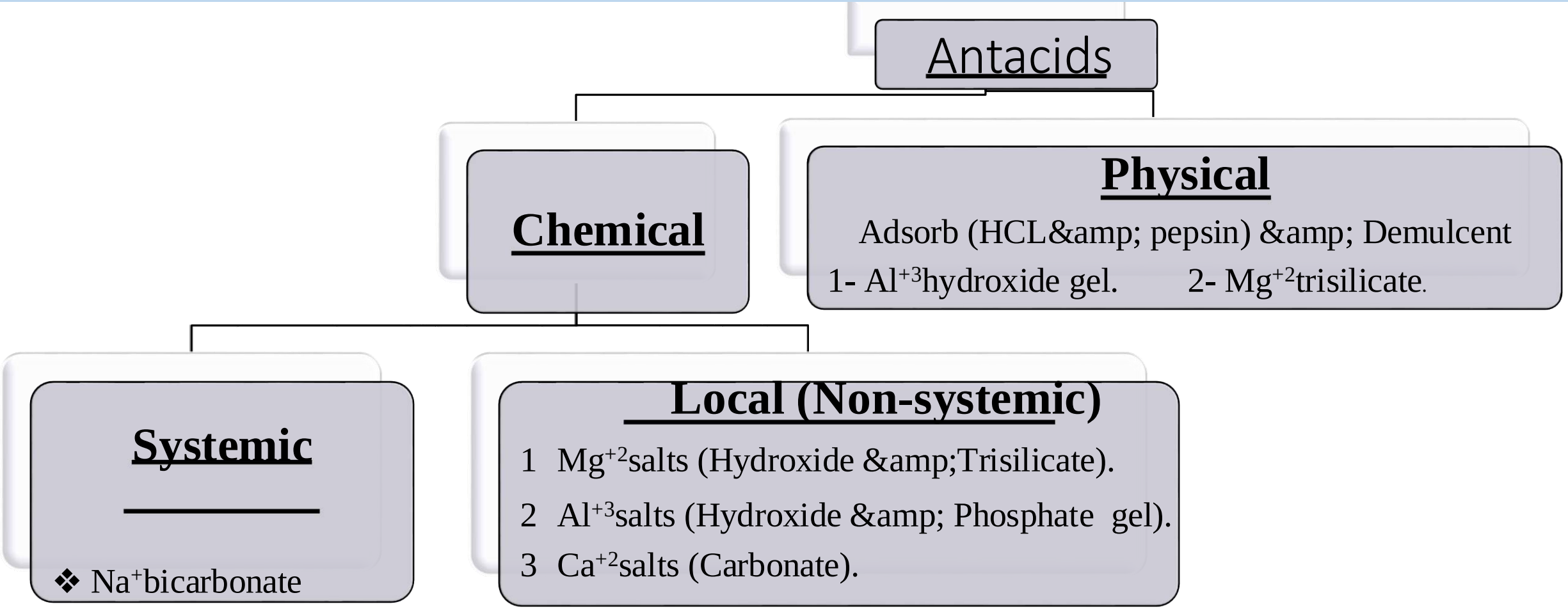
Uses: Prevention of NSAIDs-induced ulcers in high-risk patients.

Side effects:

1.Diarrhea & abdominal pain (10-20%).

2.Uterine contraction (abortion & vaginal bleeding).

2- Neutralization of HCL



Antacids

Pharmacological actions:

❑Antipeptic effects:

Reduction of gastric acidity will suppress the activity of pepsin

Activity decreases as PH increases above 2 and is Irreversibly inactivated at PH 7

Al+3 containing antacids → adsorb pepsin.

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

Gastro- intestinal motor activity:

↑ PH (of gastric content) → ↑ gastric motility (gastrin) → ↑ LESP.

Al+3 → relax smooth muscle of stomach (astringent) → constipation.

Mg+2 → ↑ cholecystokinin → ↑motor activity.

Mg+2 → osmotic laxative effect.

Magalderate [rioper]

(AL hydroxide + magnesium hydroxide)

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

(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

B + M + A → 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). · Clarithromycin (5oomg three times daily).

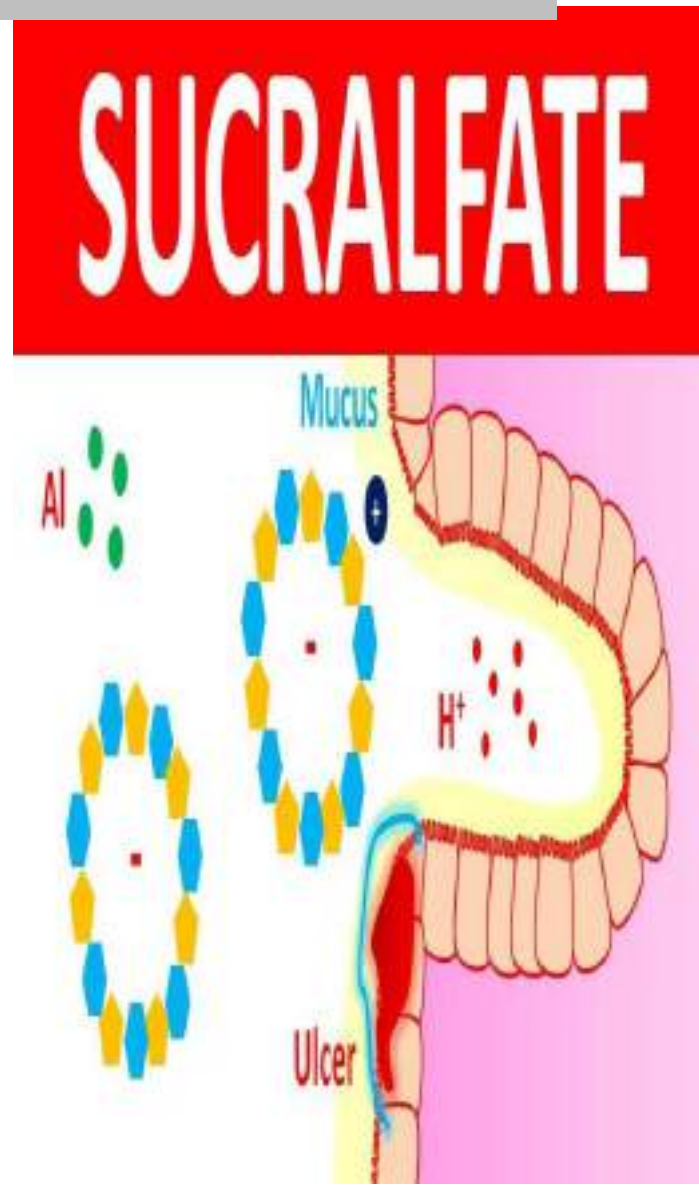
Peptic ulcer & helicobacter pylori

Quadruple	. Drugs that eradicate H Pylori + Anti-secretory drugs.
Triple	. M + A + Antisecretory drugs. (Metronidazole+ Amoxicillin or Clarithromycin+ PPIs
Dual	. Amoxicillin + Omeprazole . Clarithromycin + Omeprazole

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

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) Decrease stool frequency and fluidity used in diarrhea of acute infections(travelers' diarrhea)

Side effects

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

N.B.

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

C- Carbenoxolone (biogastrone)

- Synthetic derivative of liquorice.
- Mineralocorticoid activity → aldosterone-like side effect (salt and water retention).

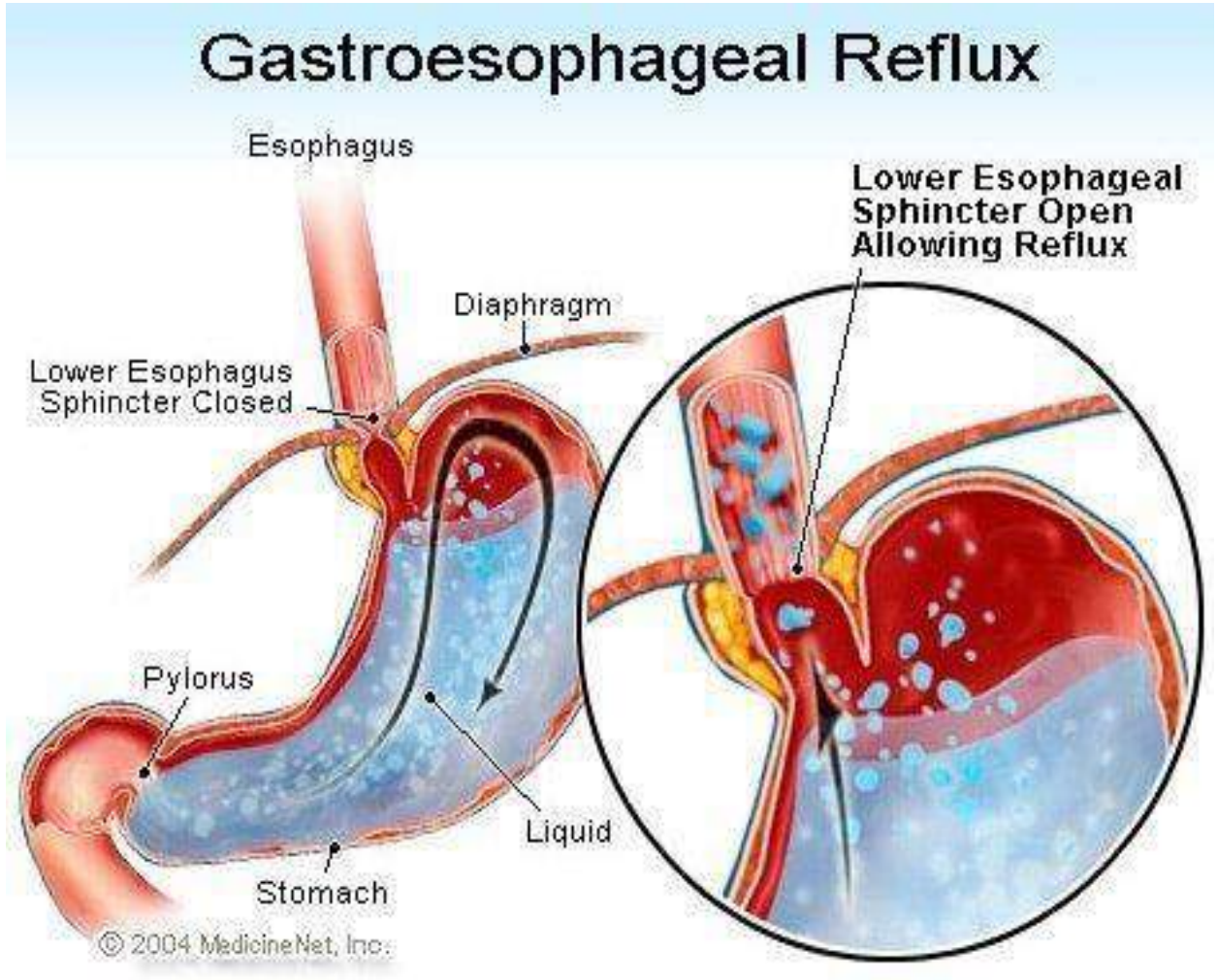
Mechanism of action:

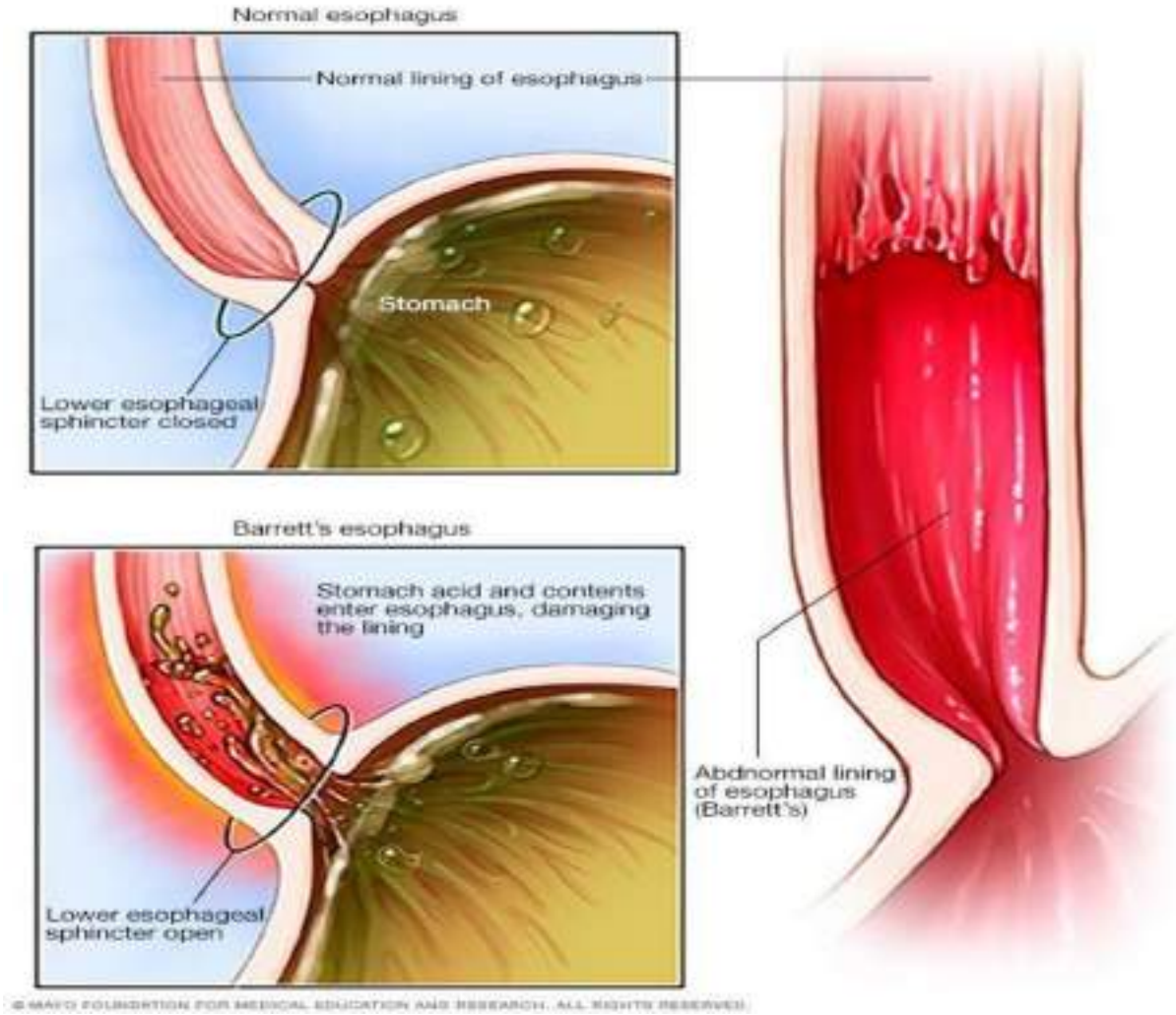
↑Production, secretion & viscosity of intestinal mucus.

Side effects:

Na+ & water retention, hypokalemia & hypertension.

Gastro-Esophageal Reflux Disease (GERD)





General guidelines for medical management of GERD:

- **Antacids** are recommended only for patients with **mild infrequent episodes of heartburn**.
- **Non-erosive GERD** may be treated successfully with **intermittent courses of PPIs or H2 antagonists taken as needed (on demand) for recurrent symptoms**.
- **PPIs are the most effective agents** for the treatment of **non-erosive & erosive reflux disease, and esophageal complications & extraesophageal manifestations of reflux disease**.
- **Extra esophageal complications of reflux disease** (asthma, chronic cough, laryngitis, and noncardiac chest pain): sustained acid suppression with **twice-daily PPIs for at least 3 months** is used.
- **GERD symptoms recur** in over 80% of patients within 6 months after discontinuation of PPIs.
- - For patients with **erosive esophagitis or esophageal complications**, **long-term daily maintenance therapy with a full dose or half-dose PPIs** is usually needed.

Medical management according to severity of GERD

Stage I	**S**poradic 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	Frequent symptoms more than 2-3 episodes/week (with or without esophagitis). ▪ Although higher doses of H_2 antagonists increase healing rates, PPIs are preferred.
Stage III	Chronic, unrelieved symptoms or immediate relapse after stopping therapy. ▪ PPIs either once or twice daily.

GERD & pregnancy:

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

GERD& children:

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

Role of prokinetics in treatment of GERD:

Acid reflux is associated with transient LES relaxation that occurs in absence of a swallow. 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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