Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

○ Slide ● Sheet ○ Handout ○ Other

☐ Anatomy ☐ Embryology

☐ Physiology ☐ Histology

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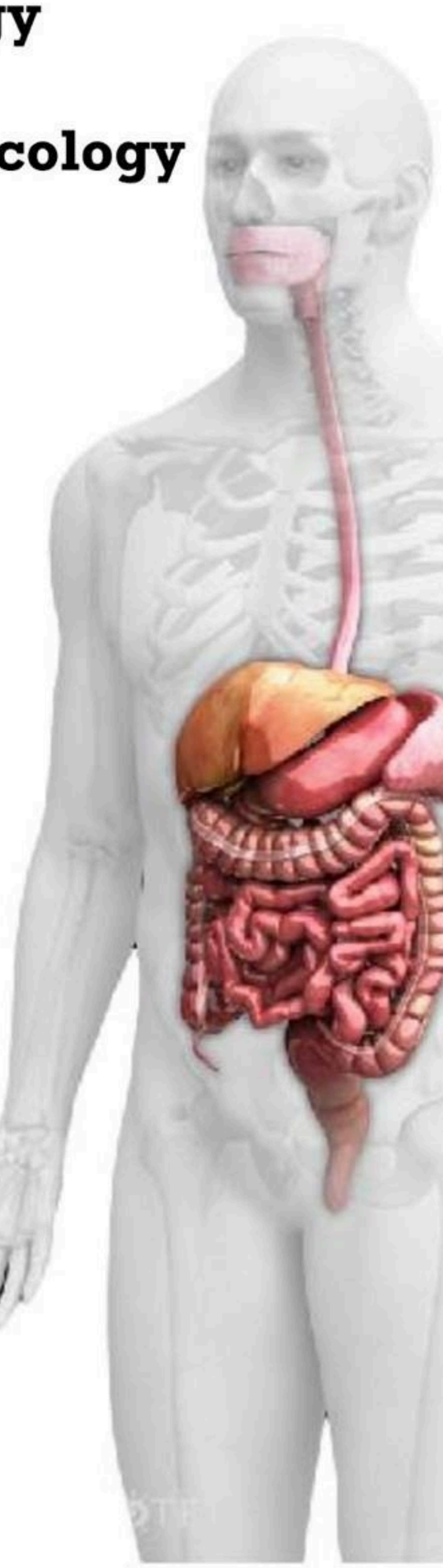

Sheet #: 1

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Date: 22-4-2015

Price:

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Drugs Used in the Treatment of Gastrointestinal Diseases

There're some questions at the end of the sheet, please try to see them even if you don't study sheets.

* Physiology of gastric secretions:

- Gastric acid secretion starts by the stimulus of Ach, gastrin or histamine which stimulates the parietal cells to translocate the proton pump (H+/K+-ATPases) toward the apical cell membrane. (See figure1)

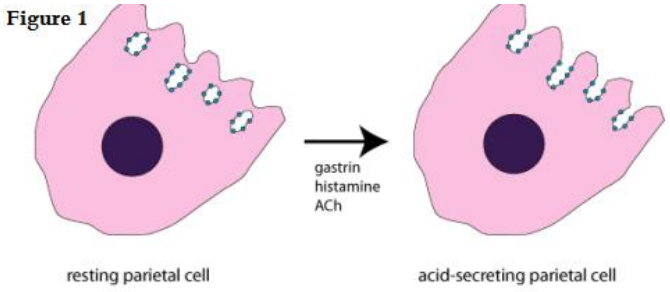

Figure 1

- Usually parietal cells secrete 2 liters of acid per 24 hrs. Optimal pH (between 1.8-3.5) for the function of the digestive enzyme pepsin.

- The proton pump which is called is H+/K+-ATPases; because it allows the exchange between hydrogen and potassium ions, releasing the hydrogen to the lumen. The energy needed for this process is derived from ATP hydrolysis.

- For the formation of HCl we need to release Cl^- and H+. However, these ions aren't secreted together; they're secreted separately and then mixed in the canaliculi.

* Stimulants of acid secretion:(figure 2)

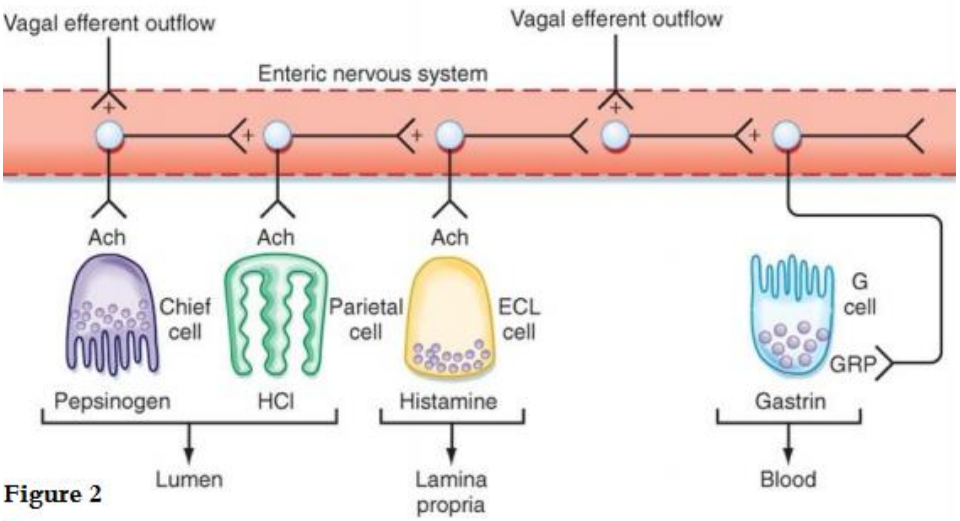

Figure 2

We have 3 stimulants:

1- Ach → usually comes from the vagus nerve (parasympathetic nerve) and stimulates ENS. Ach stimulates 3 cells: **A.** Chief Cells that release pepsinogen which is later on converted into pepsin. **B.** Parietal cells which release the acid.
Ach also stimulates the release of:

2- Histamine from ECL (enterochromaffin - like) cells. (consider it as point "C." also)

3- (here the dr. said that "also Ach stimulates the release of") but I think that Gastrin is released as a response to GRP rather than Ach)→ "according to the pic and what I read in wiki"Gastrin, which is released by G cells, stimulates the acid secretion.

* On the other hand, D cells secret somatostatin which inhibits the acid secretion. Once the pH of the stomach gets too low, somatostatinis released; it inhibits the gastrin release, and inhibits the acid secretion directly.

* There are three phases in the secretion of gastric acid:(figure 3)

1- Cephalic Phase:

In this phase, there's still no food in the stomach ,but any thought about food, smelling food, seeing food, hearing someone talking about food→all those cause stimulation of the vagus nerve → stimulation of ENS → releasing of gastrin and histamine →parietal cell stimulation →acid secretion.

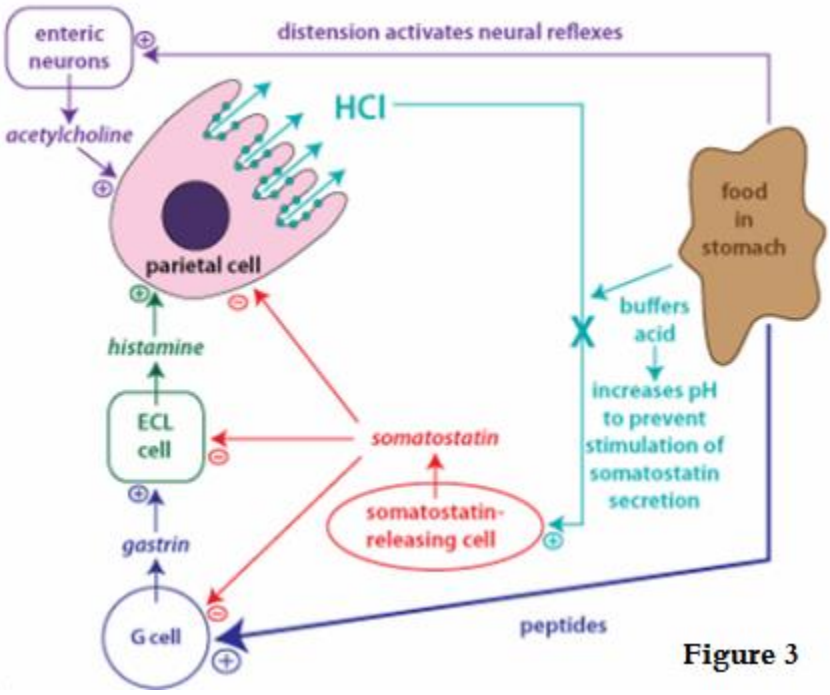

Figure 3

2- Gastric Phase:

In this phase, there's food in the stomach. The presence of food stretches the stomach walls, this stretching (distension) effect stimulates the ENS → stimulate acid secretion.

At the same time, food that is partially digested (peptides and amino acids) directly stimulate the gastrin release from G-cells → this gastrin stimulates the enterochromaffin-like cells to release histamine →histamine through binding to (stimulating) H2 receptors on the parietal cells, it stimulates the acid secretion.

Also, there is food or part of digested food in the stomach which act as a buffer. This buffer prevents the decrease in pH; because if the pH becomes too low, somatostatin secretion -which inhibits the acid secretion- will be stimulated. So the food buffers the pH,prevents the inhibition of acid secretion until the process is completed and until the food reaches the stomach "the dr. said stomach but I think it must be duodenum".

3- Intestinal Phase:

Once the chyme reaches the duodenum, it activates negative feedback mechanism to reduce acid secretion.

* Peptic ulcer:

- Ulceration is: a damage/defect in the lining of the stomach/duodenum. When acid touches this damaged part, pain and other symptoms will develop.
- Mostly, ulcer occurs in duodenum ,but also ulcer of the stomach may happen.
- Mainly, ulcer of the stomach is due to intake of Non-Steroidal Anti-Inflammatory Drugs like aspirin and ibuprofen.

* Causes:

In the past, peptic ulcer was treated with antacids and later on with H2 receptor antagonist. The main cause of ulcer is *H.pylori* bacteria. Unless this microbe is eradicated, ulcer will continue even after healing.

So the causes are:

1. Helicobacter pylori→ most common cause of ulcer.
2. Some drugs like: Aspirin and all NSAIDs. These drugs inhibit the synthesis of prostaglandins, which are important for the infection of stomach mucosa.
   So once this structure is removed, ulcer occurs.
   Other drugs include: Hydrocortison /corticosteroids.
3. Smoking.
4. Stress.
5. Some carcinomas like: Zollinger Ellison syndrome which is a rare gastrin secreting tumor.(High gastric secretion→ulcer)

* 2 factors involved in ulcer formation:

1- Acidity
2- The causative organism which is *H.pylori*.

So trying to treat ulcers, these factors must be taken in consideration.

- The H.pylori causes inflammation that stimulates the inflammatory cascade (including neutrophils, lymphocytes, and cytokines) and causes damage.

* Symptoms:

1. Burning pain in stomach between meals. When the stomach is full → no problem. Once the stomach is empty "between meals" → there's pain.
2. Bloating, heartburn, nausea or vomiting.
3. In severe cases, bleeding happens → vomiting of blood.
4. Stool appears dark or black.
5. Weight loss & severe pain in the mid to upper abdomen.

* Complications:

In addition to having a miserable life because of the constant pain, the patient may develop several complications including:

1. Gastrointestinal bleeding, and sometimes sudden bleeding which may be excessive and can cause death. (Sudden large bleeding can be life-threatening).
2. *H.pylori* is a cause of cancer (as a risk factor).
3. Perforation (hole in the stomach wall) →Penetration.

So complications can be very severe.

* Treatment options:

- We have to deal with both; the acid and the bacteria.

⇨ HOW TO DEAL WITH THE ACID ?!

1. Reduce acid secretion
2. Neutralize the already existed acid in the lumen by the use of antacids.
3. Protect the mucosa from acid destruction.

1. Reduce acid secretion:

Inhibition of acid production:

We know that Ach is a key factor in this process →thus we must inhibit it.

- So in the past, they use atropine as an anti-cholinergic drug, but the use of these agents requires giving high doses of atropine.

Also, pirenzepine (M1 antagonist).

But still there're a lot of side effects because we have to give high doses. Those side effects include: constipation, blurred vision, cycloplegia(paralysis of the ciliary muscle of the eye), urinary retention, no sweating.

In the past, they've used surgery to cut the vagus nerve branches, but now these drugs are not used anymore; because we've very effective drug.

- Since we have histamine release and it acts at H2 receptors → we can use H2 receptor antagonist which acts on these receptors and reduce the acid secretion. Also, histamine can act in the periphery at the proton pump → so we can use proton pump inhibitors (PPIs) which are very effective drugs that inhibit acid secretion. (See figure 4).

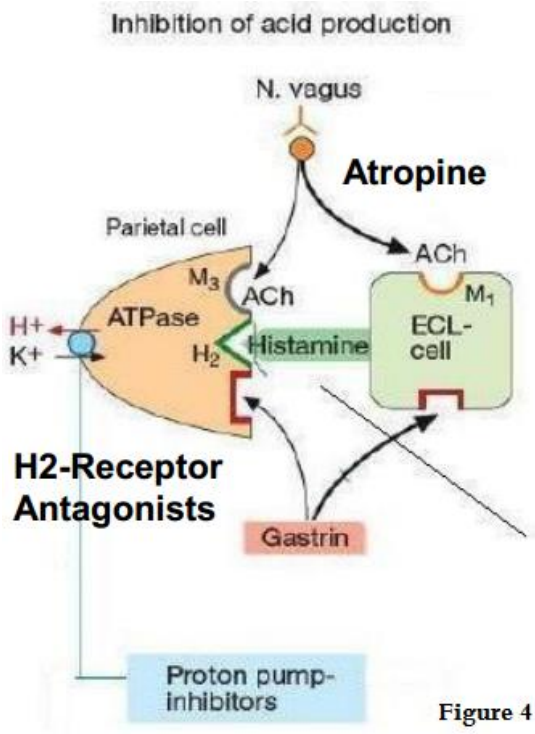

Figure 4

2. Neutralize the already existed acid in the lumen by the use of antacids.

"We'll talk about it in minutes"

3. Protect the mucosa from acid destruction:

Another type of treatment is providing protection to the mucosa of the stomach. Drugs called **Sucralfate** can coat the ulcer and provide a barrier between the acid and the ulcer → this allows the ulcer to heal gradually.

⇨ NOW, HOW TO DEAL WITH THE BACTERIA ?!

Of course we have to treat the bacteria by antibiotics. Usually a combination of antibiotics is used so that we can be sure of the effectiveness of treatment and try to prevent the resistance of the bacteria to antibiotics.

Let's return back to discuss the 2nd point of how to deal with the acid which is "to neutralize the acidity":

- To neutralize the acidity, we can use **ANTACIDS** which have been used for so many years; they're cheap & effective ,but should be taken frequently and usually these drugs have nonprescription remedies for treatment of heartburn & dyspepsia.

- Many people who take it don't have full ulcer → so if we're giving the drug 1 hour after a meal; it will effectively neutralize gastric acid for up to 2 hours.

- The best agents "slowly acting agents" are **Aluminum hydroxide** "$Al(OH)_3$" and **Magnesium hydroxide** "$Mg(OH)_2$" → they have the advantage that they act slowly so their effect is extended. Also, the drug produces ....(18:22,can't hear what the dr. is saying) which reach the cells of the stomach and cause belching and bloating.

- All aluminum salts can cause constipation and interfere with the absorption of many drugs.

- All antacids cause diarrhea. They reduce the gastric acid release but also cause some acid rebound.

Acid rebound:
The hypersecretion of gastric acid that may occur after the initial buffering effect of an antacid. It occurs most noticeably when antacids containing calcium carbonate are used.

- **Magnesium trisilicate** which is a slow-acting antacid.

- Usually used as combination. They put aluminum hydroxide with Magnesium hydroxide and in this case there's NO constipation or diarrhea.

- **Calcium carbonate** which is cheap but has a problem since continuous, excessive use can cause acid rebound and milk-alkali syndrome (milk → because of the intake of calcium), increase of serum calcium, phosphate, urea, nitrogen,creatinin, bicarbonate levels. It also produces carbon dioxide"CO_2" which stretches the wall of stomach and cause (20:21, can't hear what the dr. is saying).

- **Sodium bicarbonate**is not recommended and has very fast action, so it causes a fast relief but it's completely absorbed; the sodium is absorbed and the bicarbonate is absorbed and you know excessive sodium is bad for the body "drs advice to avoid the 3 whites: flour, sugar and salt". Also excessive salts potentially cause metabolic alkalosis. CO2 results in gastric distention and belching.

H2-receptor antagonists:

- They were developed in 70s. They reveal the treatment (22:42).

- The first one was Cimetidine→ very effective but associated with many bad side effects☹

- There are newer drugs such as Ranitidine, Famotidine and Nizatidine; they don't have the problem of Cimetidine and they're very effective.

- You can see in figure 1,they inhibit the association between histamine and H2-receptors.

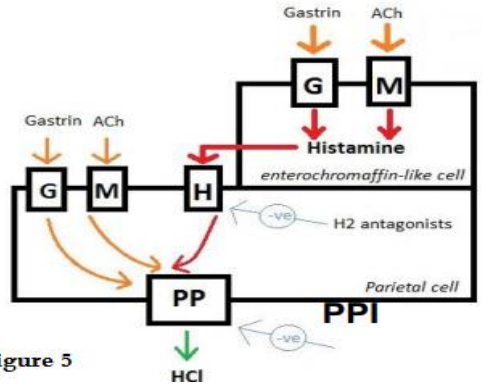

Figure 5

- Cimetidine, Ranitidine, Famotidine and Nizatidine are rapidly absorbed from intestine. Some of them undergo first pass effect so less effect of these drugs appear in the blood. However, Nizatidine has little first-pass metabolism. Duration of action:6–10 hours, usually given twice daily.

- These drugs are most effective at inhibiting the *nocturnal acid secretion* (acid secretion during sleeping) ,but less active against *meal stimulated acid secretion*.Because it doesn't affect gastrin and Ach (which stimulates the meal-stimulated secretion).So 90% inhibition of nocturnal acid (depends on histamine). Inhibit 60% of day-time, meal stimulated acid secretion. Overall, 60-70% inhibition of total 24-h acid secretion.

- Those were no. 1 used drugs in the treatment of peptic ulcer until PPIs were developed.

- **Clinical uses:**

1. **Gastroesophageal Reflux Disease (GERD):**
   Normally, closure of the lower esophageal sphincter prevents the reflux of acids from the stomach up to the lung. Some people have weakness of this sphincter, so the acidic food in the stomach goes up and may reach the lung. These people are advised not to eat late at night and to use 2-3 pillows when they sleep. H2 antagonists are useful in these cases if they're taken prophylactically before meals. However, in erosive esophagitis (where the acids reach the esophagus and cause erosion, damage, and ulcer formation) H2 antagonists are not effective(healing is less than 50%); hence PPI are preferred.
2. **Non Ulcer Dyspepsia:**
   Over-the-counter for anytime even if the person doesn't have ulcer, but agents for treatment of intermittent dyspepsia not caused by peptic ulcer.
3. **Prevention of Bleeding from Stress-Related Gastritis:**
   Stress is a cause of gastritis and gastritis can develop into cancer. Some patients, who have cancer or a chronic dangerous disease, may have severe stress and this stress will cause gastritis and gastritis will cause ulceration, bleeding and severe pain. These people are given IV(Intra Venous) H2 antagonists which are preferable over IV PPI ,because of their proven efficacy and lower cost. However, PPIs are very effective and given by nasogastric tube.
4. **Peptic Ulcer Disease:**
   The place of H2 antagonist is shifted from the 1st line to the 2nd. And PPIs become in the 1st line. So they (H2 antagonist) are replaced by PPI.
   * Healing rate is more than 80-90% after 6-8 wks. But in case we didn't eradicate *H.pylori*, they're not effective. Also, they're not effective if the patient continues to take NSAID.

- **Adverse Actions:**

- They're very safe but patients might develop *mild side effects* such as: Diarrhea, headache, fatigue, myalgias, and constipation. BUT:

-Cimetidine has more side effects and may cause gynecomastia & impotence in men (anti-androgenic effects) and galactorrhea in women.

Gynecomastia: benign enlargement of breast tissue in males.
Impotence: sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual activity.

Galactorrhea: spontaneous flow of milk from the breast, unassociated with childbirth or nursing.

- **Drug Interactions:**

- These drugs are metabolized in the liver by cytochrome P450. And this enzyme family is important for many drugs' metabolism →so interference in metabolism of many drugs→drug-drug interaction (interference).
-Cimetidine inhibits cytochrome P450 enzymes so can increase half-life of many drugs.(From slides).
- Ranitidine is 4-10 times less effective in this liver enzyme.
- Nizatidine and famotidine binding is negligible (have no action related to this enzyme thus no drug-drug interaction).

Proton Pump Inhibitors (PPIs)

They're the most widely used drugs since the stomach problems are very common. They're very effective and safe. Include: Omeprazole (oral), Rabeprazole (oral), Lanzoprazole (oral and IV), Pantoprazole (oral and IV), Esomeprazole (oral and IV).
These are prodrugs, by themselves they're not active. They have to be converted in the parietal (not sure) cells into the active form, the active form covalent bond with the proton pump thus cause complete inactivation/inhibition of the pump. But also these agents are destroyed by the acid in the stomach so they're formulated in

a way that they're not released directly in the stomach, instead released in the intestine. Because they've to get to the intestine to get absorbed →this means a delay in their action.

Sometimes when the patient has ulcer bleeding and we want sth to act fast → we have Immediate Release Suspension → immediate: releases it in the stomach not in the intestine but in order to protect it from acidity we give sodium bicarbonate (a suspension that contains sodium bicarbonate to protect the drug from acid degradation) and that results in a faster response.

- These are Lipophilic weak bases. When they get absorbed in small intestine, they are delivered to parietal cell through the blood and there they're protonated and "trapped" in acidic canaliculi then concentrated more than 1000-fold concentration in blood.
- After conversion into the active form which covalently binds the H+/K+ ATPase enzyme and permanently inactivates it.
- Although they've short half-lives but their effect lasts for 24 hours.
- Now the body has to synthesize new proton pump to reverse those that have been inactivated, and at least 18 hours are required for synthesis of more new pump molecules.
- So these are long acting, very effective drugs so they inhibit acid secretion whether it's meal-stimulated or nocturnal; because they act directly on the pump itself. It's about 90-98% of 24-hour secretion.
- The full inhibitory action is not seen immediately; it takes about 2-3 days to fully develop the complete inhibition of the acid.Complete inhibition = 90-98% of the secretion. The remaining amount is enough for the digestion of food.

- **Clinical uses of PPIs:**

1. **Gastroesophageal Reflux Disease (GERD):**

   PPIs are the most effective agents in all forms of GERD. We've seen that H2 antagonists have an effect but don't lead to cure but PPIs are very effective and they're taken daily.

2. **Nonulcer Dyspepsia:**
   We can use PPIs but it's really a waste of money "they're expensive"
3. **Stress- Related Gastritis:**
   In critically ill patients there's suffer andgreat stress that cause gastritis, ulcer, bleeding. We can use PPIs just as omeprazole which is given by nasogastric tube. If we don't have this tube, we use IV H2- blockers are preferred because of their cheaper price and their proven efficacy.
4. **Gastric acid hypersecretory states**, including **Zollinger -Ellison syndrome**:
   They're very effective. Usually high doses of omeprazole are given.

- Note: All these agents have the same efficacy.

5. **Peptic Ulcer Disease:**
   One of the most important uses is the treatment of Peptic Ulcer Disease. They (PPIs) have some anti-microbial actions. They heal more than 90% of cases within 4-6 weeks of continuous use of the drug.

H.Pylori - associated ulcers:

* We've mentioned before that H.pylori has to be eradicated, so in this case although they have anti-microbial activities, they are used in combination with anti-biotics to help in lowering the dose of antibiotics (MIC"minimal inhibitory concentration of the antibiotic is reduced).

**** Triple therapy:***

-Three drugs are given at the same time.

- PPI twice daily + Clarithromycin 500 mg twice daily +Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily→ For one week, after this week continue the treatment with PPI alone.

NSAID-associated ulcers:

We have ulcers caused by the use of aspirin and NSAIDs. Healing occurs despite of the continuous NSAID use. However, H2 antagonist if you continue using them, they become non-effective.

So if somebody has chronic condition that requires continuous use of NSADs, they give him PPI → so that he will not develop ulcer (there's healing despite continued NSAID use and also they're used to prevent ulcer of NSAIDs "in patients who have arthritis and have to use NSAIDs).

Rebleeding peptic ulcer:

Oral or IV. High pH may enhance coagulation and platelet aggregation.

- **Adverse Effects:**

- They're safe but may cause some headache, diarrhea, abdominal pain, nausea &dizziness.
- There are some complications that result from the reduction of the gastric acidity:
  1. Reduction of cyanocobalamine(vitamin B12) absorption. As you know vitamin B12 exists in meat and proteins (it's attached to proteins). For B12 to be separated (detached) from these proteins, it needs an acid.So if there's no acid → vitamin B12 will not be detached from proteins → it will not be absorbed →deficiency of vitamin B12.
  2. Increased risk of GI and pulmonary infection. If somebody eats sth that's contaminated with bacteria, the acid in the stomach is effective in killing many bacteria (it doesn't mean a complete killing but the majority is killed in the stomach by the high acidity). So in the case where there's no acidity → bacteria won't be killed → bacteria will cause disease and if it goes up to the lung it'll cause pneumonia, pulmonary infections…

- Also the chronic use of these drugs causes increase in gastrin lipid secretion →which causes chronic inflammation in gastric body →Atrophic gastritis and intestinal metaplasia.
- Until now there's no cancer associated with the use of these agents.

- **Drug Interactions:**

May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.

Mucosal Protective Agents:

- Normal protective mechanisms:
  - Mucus secretion and bicarbonate secretion.
  - The microcirculation provides bicarbonate.

It depends on prostaglandins which enhance gastric mucosal blood flow and increase mucous and bicarbonate secretion

* You can notice in the pic that: in mucosal cells → pH = 7 alkaline, while it's equal to 1-2 in the lumen.

  - Restitution: to repair the damage.

Sucralfate:

- It's a salt of sucrose complexed to sulfated aluminum hydroxide. In the stomach, it breaks down into sucrose sulfate(strongly negatively charged) and an aluminum salt. The negatively charged sucrose sulfate is attracted to positively charged proteins in the base of ulcers or erosion, forming a coat around the ulcer which makes a physical barrier that prevents the acid from attacking the ulcer thus promotes healing of the ulcer, it also stimulates mucosal prostaglandin and bicarbonate secretion.
- Its action is for 6 hours.
- Minimal absorption happens (Less than 3% of intact drug and aluminum is absorbed).

- **Clinical uses:**

1 g four times daily on an empty stomach (through a nasogastric tube) reduces the incidence of upper GI bleeding in critically ill patients hospitalized in the intensive care unit.

Why we don't use it with any patient ?!we use it but only for prevention of stress-related bleeding because acid inhibitory drugs may increase the risk of nosocomial pneumonia (an infection of the lungs that occurs during a hospital stay).

- **Adverse Actions**:"little"

- Because it's not absorbed→ there are no systemic adverse effects.
- All the constipation (2%) is due to the aluminum salt.
* Caution in renal insufficiency.

- **Drug Interactions:**

Sucralfate may bind to other medications, impairing their absorption.

GOOD LUCK

We haven't finish :P please check the questions in the next 2 pages

1. Which drug regimen is currently being used to treat peptic ulcers?
   A) Proton pump inhibitors or H2-blocker and antibiotics
   B) Calcium channel blockers and antibiotics
   C) Antacids and proton pump inhibitors

The answer is: A

2. Which two classes of drugs are used to reduce acid in gastroesophageal reflux disease?
   A) Proton pump inhibitors and H2-blockers
   B) Proton pump inhibitors and H1-blockers
   C) Antibiotics and antacids

The answer is: A

3. What are the primary etiologies of gastric ulcers?
   A) Stress
   B) Spicy foods
   C) The organism Helicobacter pylori
   D) Chronic use of the nonsteroidalantiinflammatory drugs (NSAIDs), especially in elderly adults
   E) All of the above
   F) c and d

The answer is: F

4. All of the following drugs are H2-receptor blockers except one. Which one is the exception?
   A) Cimetidine (Tagamet)
   B) Famotidine (Pepcid)
   C) Ranitidine (Zantac)
   D) Omeprazole (Prilosec)
   E) Nizatidine (Axid)

The answer is: D

5. What action does smoking have on gastric acid secretion?
   A) Smoking decreases gastric acid secretion.
   B) Smoking increases gastric acid secretion.
   C) Smoking does not affect gastric acid secretion

The answer is: B

6. All of the following are adverse drug effects of cimetidine (Tagamet) except one. Which one is the exception?
   A) Slurred speech
   B) Delusions and confusion
   C) Increased sperm count and increased sexual potency
   D) Headache
   E) Gynecomastia

The answer is: C

7. Cimetidine interacts with other medications, resulting in a delay in elimination and an increase in serum levels of some drugs, possibly producing toxicity by the following mechanism:
   A) Inhibition of the first-pass effect
   B) Inhibition of glomerular filtration
   C) Inhibition of liver microsomal enzymes
   D) Inhibition of biliary excretion

The answer is: C

8. Advantages of proton pump inhibitors over H2-receptor blockers in the treatment of gastric ulcers include:
   A) More rapid healing
   B) Tolerance does not occur
   C) Lower cost
   D) All of the above
   E) a and b only

The answer is: E

9. All of the following can be used as antacids except:
   A) Sodium bicarbonate
   B) Calcium carbonate
   C) Aluminum salts
   D) Mineral oil

The answer is: D

Another ...

GOOD LUCK