PASSION ACADEMIC TEAM

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Sheet# 6

YU - MEDICINE

GASTROINTESTINAL SYSTEM

Lec. Title : Treatment of The Peptic Ulcer .

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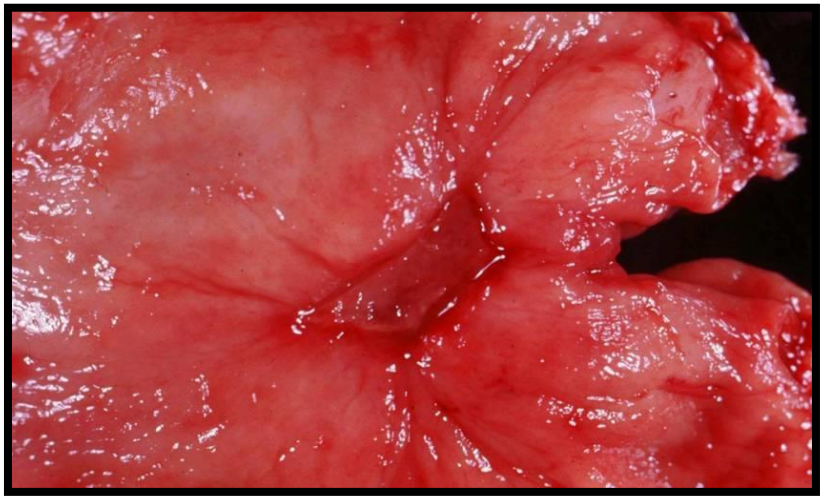
Treatment of Peptic Ulcer

Dr. Romany H Thabet

Peptic Ulcer



A breach in the mucosa of the alimentary tract, which extends through the muscularis mucosa into the submucosa or deeper.

Peptic ulcer : ulcer in stomach .

Duodenal ulcer : ulcer in duodenum .

} Gastric ulcers happen in mucosal lining

Can be also in lower esophagus , jejunum .

Can be superficial in mucosa or deeper .

Mucosa of stomach → Mucosa

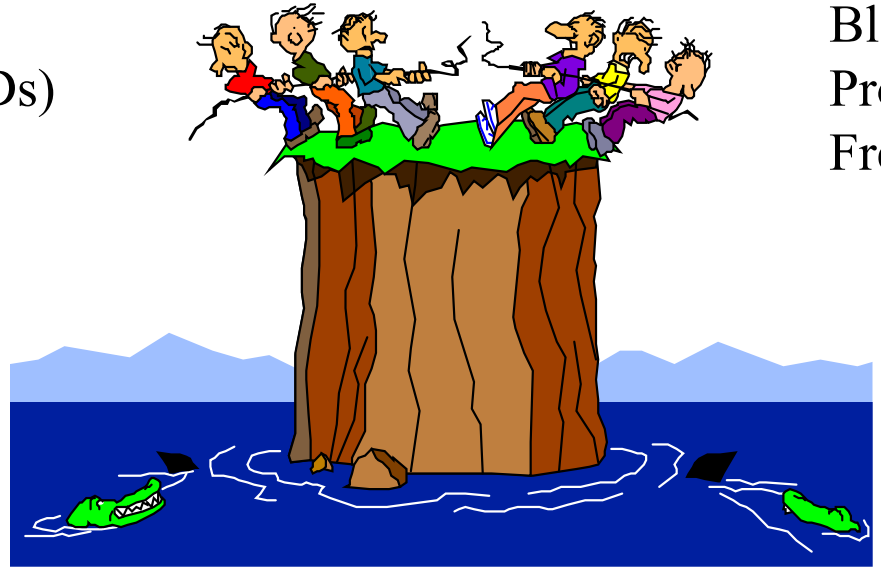
Mucosa of stomach → Bicarbonate

= Defense layers from HCL

Pathogenesis of Ulcers

Aggressive Factors

Acid, pepsin
Bile salts
Drugs (NSAIDs)
H. Pylori
Tumors (rare)



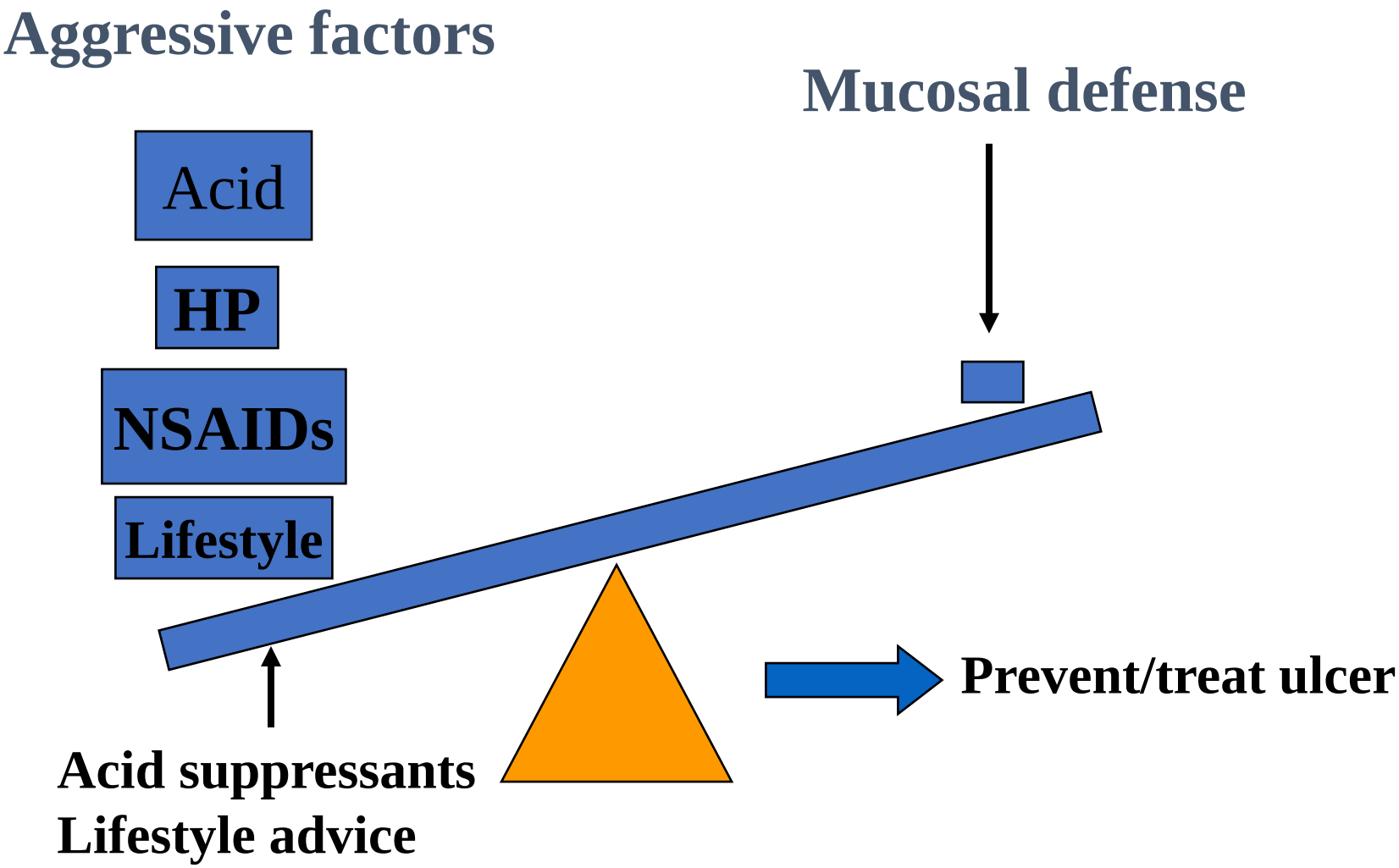
Defensive Factors

Mucus, bicarbonate layer
Blood flow, cell renewal
Prostaglandins
Free radical scavengers

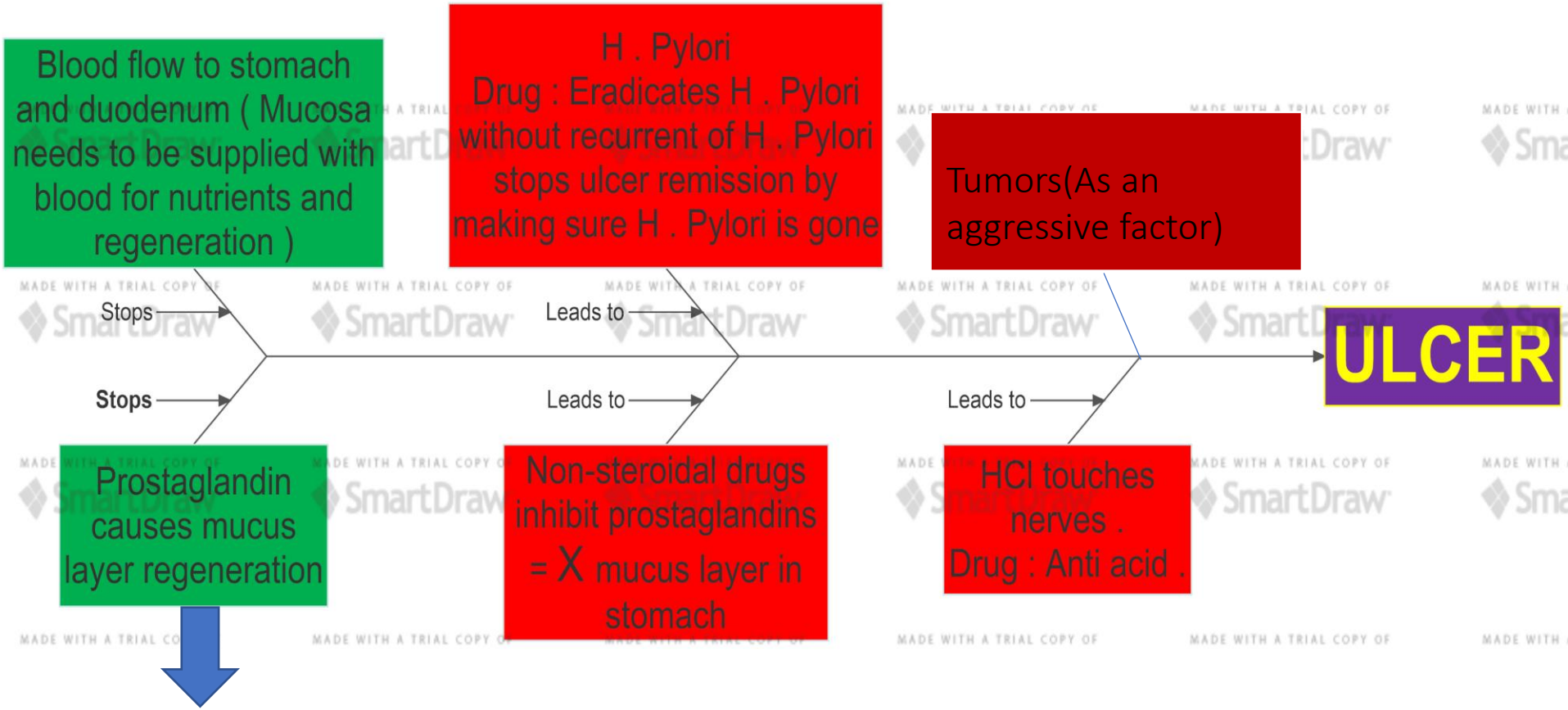
Sheet # 1

Pathology of ulcers : 3 reasons :

1. Mucosal defect : there is a layer of mucosa + bicarbonate over the stomach and duodenal lining . This layer protects against HCl .
If this layer is defective and absent , it leads to ulcers .
2. Hyperacidity .
3. H. Pylori infection : organism that only lives in the mucous and never enters the cells . It lives mostly in the mucosal stomach layer .


Aggressive factors
Mucosal defense
Acid
HP
NSAIDs
Lifestyle
Prevent/treat ulcer
Acid suppressants
Lifestyle advice

Sheet # 2

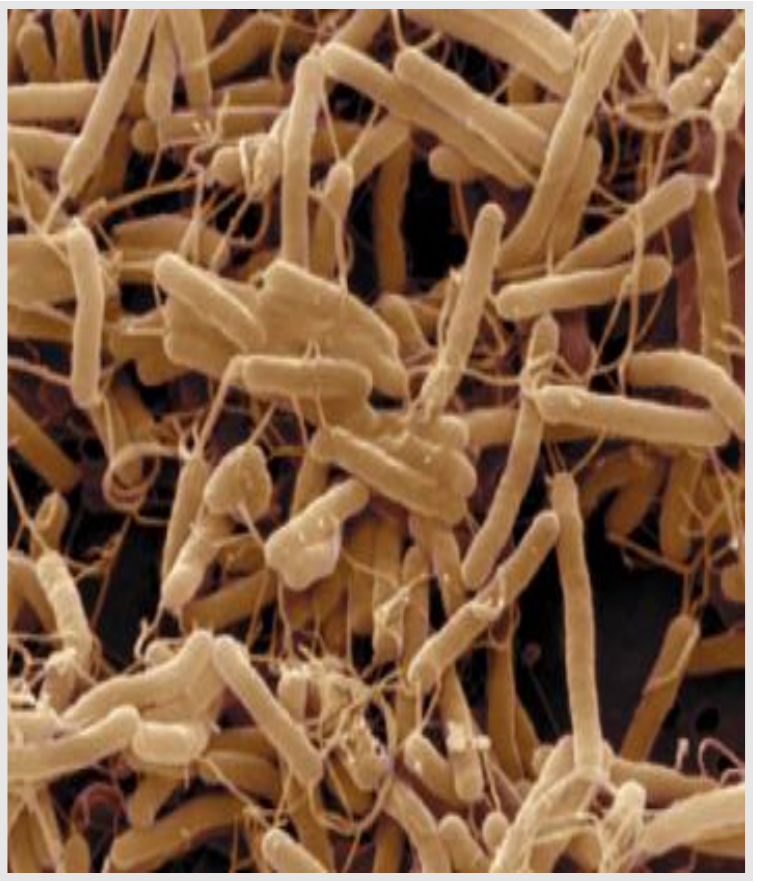


- Through Cyclooxygenase
- COX 1

Also vagal stimulation affects HCL secretion

Helicobacter pylori

- **Gram negative bacilli**
- **Do not invade cells – only mucous**
- **Break down mucosal defense**
- **Chronic Superficial inflammation**



Helicobacter pylori

- Most common infection in the world (20%)
- Positive in 70-100% of PUD patients.
- Treated by 1-2 weeks antimicrobials:
  1. Metronidazole
  2. Amoxycillin
  3. Clarithromycin
  4. Tetracyclin
  5. Bismuth salts
- Eradication of the infection usually results in long-term remission of the ulcer.

Aim of therapy

1. Relief pain(Don't use Nsaid!! Use antacid instead)

   (prostaglandins also helps because its rebuilds the mucosal layer)

1. Promote healing
2. Prevent recurrence
3. Prevent complications(such as blood loss)

Documented eradication of *H. pylori* in patients with PUD is associated with a dramatic decrease in **ulcer** recurrence to 4% (as compared to 59%) in GU patients and 6% (compared to 67%) in DU patients.

Treatment approaches include:

1. Eradicating the H. pylori infection,
2. Reducing secretion of gastric acid with the use of PPIs or H 2 -receptor antagonists, and/or
3. Providing agents that protect the gastric mucosa from damage, such as misoprostol and sucralfate. [Note: If patients are unable to tolerate the above therapies, neutralizing gastric acid with nonabsorbable antacids is an option].

Parietal cells have a proton pump(hydrogen potassium ATPase pump)

Shut this pump=No Hcl release

Parietal cells have 3 receptors
- Acetylcholine(Muscarinic type receptors)
- Histamine(H2 type receptorstimulates hcl secretion)
- Gastrin

Figure 28.1 summarizes agents that are effective in treating peptic ulcer disease.

Sheet # 3

Drugs

A. For gastric ulcer :

Reason : 1. Mucosal defect .

2. H . Pylori .

3. Hyperacidity .

Drugs : XXX antacids .

√√√ Mucosal regeneration .

B. For duodenal ulcer :

Reason : 1. Hyperacidity .

2. H . Pylori .

3. Mucosal defect .

Drugs : √√√ anti H . Pylori .

√√√ antacids .

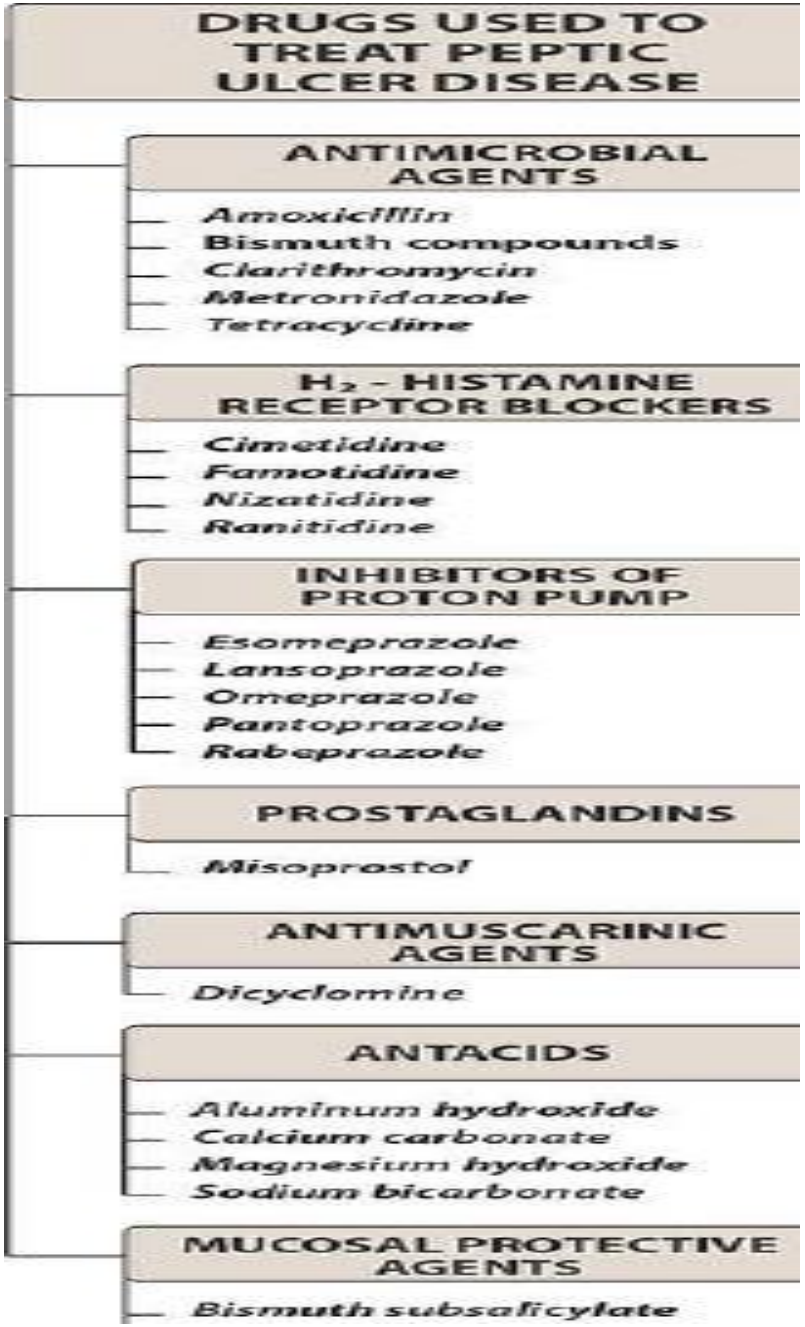
Sheet # 4

1. To differentiate between gastric / duodenal ulcers , do on endoscopy .
2. To check for H , Pylori , do a gastric analysis sample then send it to the microbiology lab .
3. Clinical picture : When talking to the patient , check for these symptoms :

    A. Gastric ulcer : Cause is mucosal defect . Patient will complain of food triggering pain the stomach . Vomiting relieves patient .

    B. Duodenal ulcer : Cause is hyperacidity . Food relieves pain , Why ?

    Food has patient . Proteins are alkaline and neutralize the hyperacidity . Vomiting worsens patient .


DRUGS USED TO TREAT PEPTIC ULCER DISEASE
ANTIMICROBIAL AGENTS
Amoxicillin
Bismuth compounds
Clarithromycin
Metronidazole
Tetracycline
H2 – HISTAMINE RECEPTOR BLOCKERS
Cimetidine
Famotidine
Nizatidine
Ranitidine
INHIBITORS OF PROTON PUMP
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
PROSTAGLANDINS
Misoprostol
ANTIMUSCARINIC AGENTS
Dicyclomine
ANTACIDS
Aluminum hydroxide
Calcium carbonate
Magnesium hydroxide
Sodium bicarbonate
MUCOSAL PROTECTIVE AGENTS
Bismuth subsalicylate

Lifestyle measures

- Stop smoking
- Avoid spicy foods, caffeine
- Avoid Aspirin and other NSAIDs
- Manage stress
- Avoid alcohol

Sheet # 5

Non - Pharmacologic therapy :

1. Stop smoking : Nicotine causes nicotinic receptor stimulation in ganglia .

   Parietal cells secrete HCl in the stomach .

   SO , 3 receptors are on parietal cells . (MI , Nicotinic , M3) .

   We need to block MI or Nicotinic ganglionic receptors to stop HCl secretion .

2. Stop non-steroidal drugs .
3. Stop steroids .
4. Stop cholinergic drugs : to not activate muscarinic or ganglionic receptors .
5. Stop stressing : Parasympathetic activation occurs duo to **SEVERE** stress .

   Stress can cause mouth ulcers , peptic ulcers .

Antimicrobial agents

- Optimal therapy for patients with peptic ulcer disease (both duodenal and gastric ulcers) who are infected with H. pylori

- To document infection with H. pylori, endoscopic biopsy of the gastric mucosa or various noninvasive methods are used, including serologic tests and urea breath tests.

- Eradication of H. pylori results in rapid healing of active peptic ulcers and low recurrence rates (less than 15 % compared with 60 to 100 % per year for patients with initial ulcers healed by traditional antisecretory therapy).

Sheet # 6

Treatment duration : 2 Weeks .

Antibiotics + Proton pump inhibitors (الدكتور ركز ع هاي النقطة كثير كثير)

Memorize antibiotics from the slides (الدكتور ركز ع هاي النقطة)

- Currently, either triple therapy consisting of a PPI combined with either metronidazole or amoxicillin plus clarithromycin

- or quadruple therapy of bismuth subsalicylate and metronidazole plus tetracycline plus a PPI, are administered for a 2-week course.

- This usually results in a 90 % or greater eradication rate.

Sheet # 7

Antibiotics against H . Pylori can not be substituted with other antibiotics .

We have 5 only that work against H . Pylori . DO NOT substitute .

Only metronidazole can be substituted with Amoxicillin .

1. Proton pump inhibitor + clarithromycin (الدكتور ركز ع هاي النقطة)
2. Proton pump inhibitor + metronidazole / Amoxicillin . If metronidazole does not work , you can give amoxicillin .

Quadruple therapy :

Proton pump inhibitor + Bismuth + metronidazole + Tetracycline .

Peptic ulcers :

Triple / Quadruple therapy for 2 weeks .

- Bismuth salts do not neutralize stomach acid, but they do inhibit pepsin and increase the secretion of mucus.

Bismuth /inhibit Pepsin / cytoProtective / inhibit H Pylori

- Treatment with a single antimicrobial drug is less effective results in antimicrobial resistance, and is absolutely not recommended.

- Switching antibiotics is also not recommended (that is, do not substitute amoxicillin for ampicillin, erythromycin for clarithromycin, or doxycycline for tetracycline).

Sheet # 8

How do Bismuth salts work ?

Bismuth salts are anti – H . Pylori , it increase the level of prostaglandins , X pepsin .

They are not anti – acids though . Just anti – pylori and pepsin .

They also have laxatives effects .

They are black in color . They cause a “ black hairy tongue “ in patients .

They are used in Quadruple therapy .

Drug therapy for peptic ulcer

- ↓ acid secretion

1. H_2 receptor antagonist
2. Proton pump inhibitors
3. Anticholinergic drugs

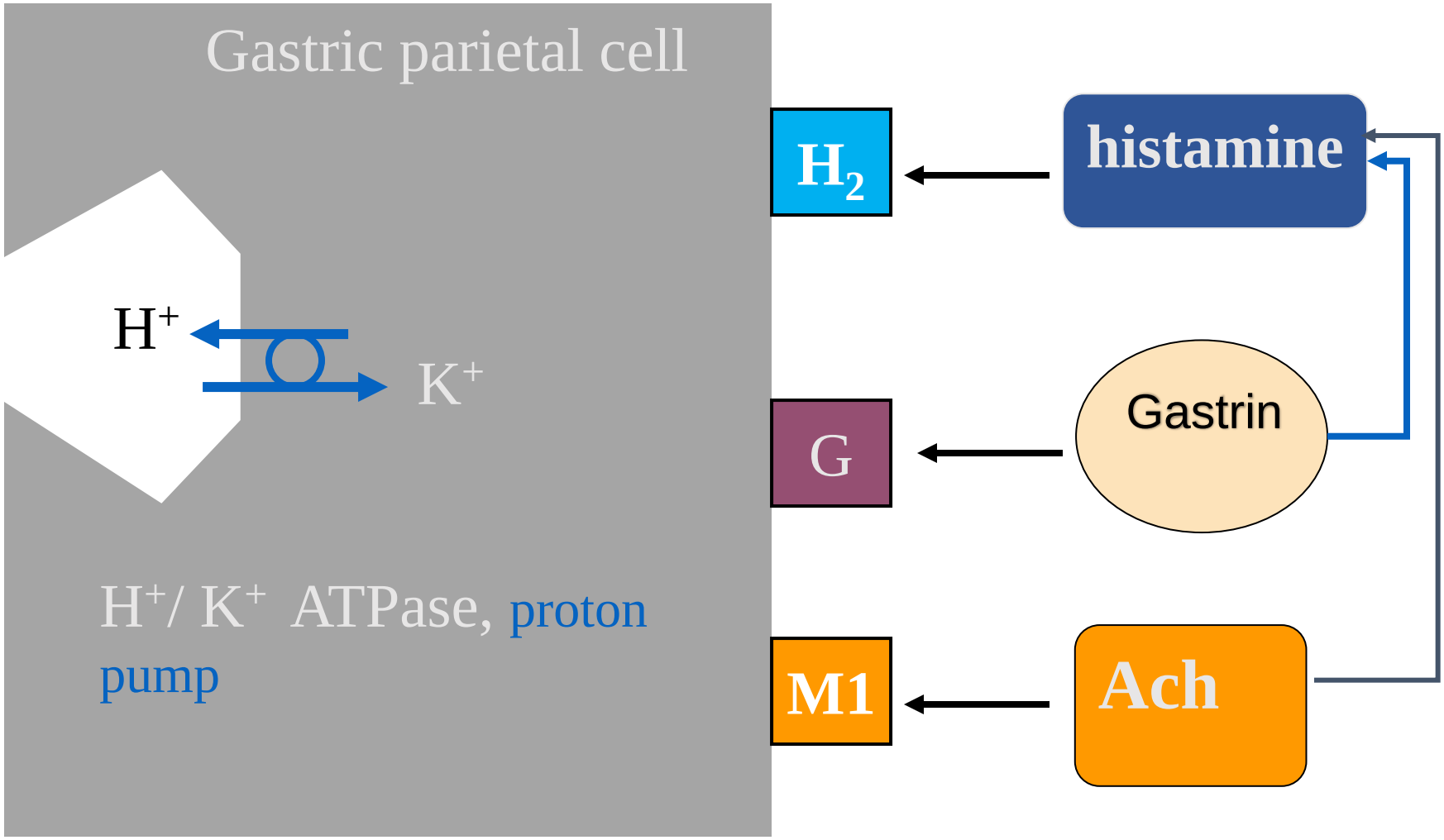
- Acid neutralization:

Antacids

- Mucosal protective factors:

1. Sucralfate.
2. Colloidal bismuth.
3. Prostaglandins
4. Carbenoxolone

P. 353 FIG 28.4



Histamine is necessary for the action of gastrin & Ach

H_2 receptor antagonists

- Act as reversible competitive inhibitors of the H_2 receptors, resulting in decrease of gastric acid secretion.
- Histamine is the predominant final mediators that stimulate parietal acid secretion.
- Particularly effective against nocturnal acid secretion
- Potently inhibit basal, food-stimulated, and nocturnal secretion of gastric acid after a single dose.
- Cimetidine is the prototype
- Used for 4-6 weeks + eradication of H.pylori

Sheet # 9

Cytoprotective Drugs .

Anta - acidic Drugs :

They neutralize acidity .

They help with pain management caused by HCl on nerves . DO NOT give painkillers . Give anta – acids .

Group A : Proton pump inhibitor .

Group B : H_2 Antagonist .

Parietal cell have receptors that get stimulated to release HCl .

Histamine receptors on parietal cells get activated by histamine . So we use H_2 antagonists .

Gastrin needs histamine to bind with its receptors .

Sheet # 10

HCl can be stimulated by food or not . It gets released during sleep .

Histamine → activates parietal cells → release HCl .

H_2 blockers help when taken at bedtime to stop HCl release during sleep .

Parietal cells have a pump (hydrogen pump) at its apical surface .

It pumps out hydrogen and takes in potassium . We use proton pump inhibitors to close this pump and stop hydrogen from getting released to bind with Chloride and form HCl in the lumen .

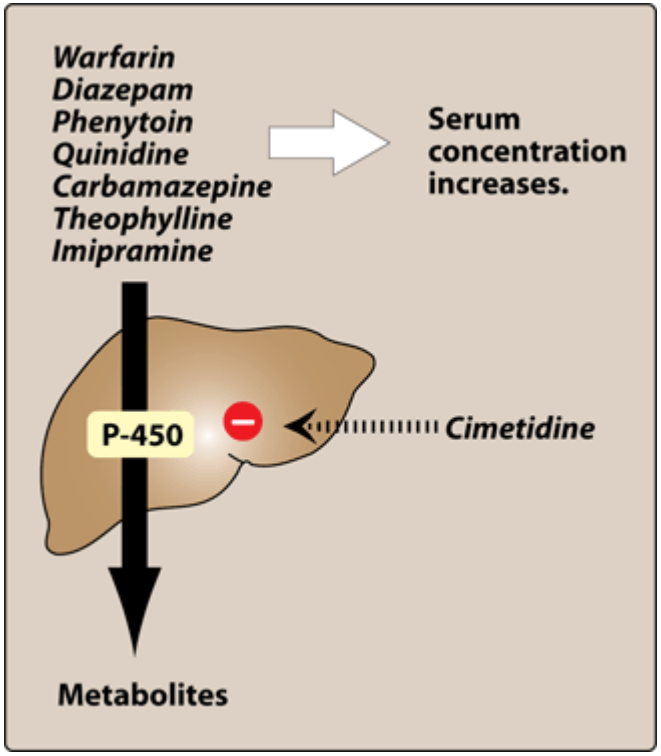
Therapeutic uses

- Peptic ulcers
- Acute stress ulcers; associated with high-risk patients in intensive care units. However, because tolerance may occur with these agents in this setting, PPIs have gained favor for this indication.
- Gastroesophageal reflux disease

Cimetidine

- Adverse effects:

1. The most common side effects are headache, dizziness, diarrhea, and muscular pain.
2. Other central nervous system effects (such as confusion and hallucinations) occur primarily in elderly patients and after intravenous administration.
3. Inhibitor of cytochrome p450, increase levels of warfarin, theophylline and phenytoin.
4. Act as androgen receptor antagonist causing reversible gynecomastia, galactorrhea and sexual dysfunction in males.



Others

- Ranitidine: Does not bind to the androgen receptors, no enzyme inhibition. longer acting. **FDA investigating Zantac for carcinogenic chemicals**
- Famotidine:

  Twice as potent as ranitidine, has longer duration of action.
- Nizatidine: eliminated principally by the kidneys. Because little first-pass metabolism occurs with nizatidine, its bioavailability is nearly 100 percent.

Proton-Pump Inhibitors

Omeprazole:

- Causes irreversible inhibition of the H^+/ K^+ ATPase, blocking the transport of hydrogen into the lumen.
- Reduces both basal and stimulated acid secretion
- Single 20mg dose ↓ acidity by 90% over 24h

Biological half life of omeprazole outlasts its plasma half life (Hit & Run).

- Prodrugs
- Must be given as enteric coated granules as it's degraded by low pH
- Absorbed in the Small intestine
- Excreted in urine and feces.

Sheet # 11

H_2 antagonists : " anything " – tidine : (Treatment length : 2 weeks , 1 extra month for remission preventing)

Cimetidine was the first H_2 antagonist but was removed duo to endocrinal effects causes CNS effects .

Ranitidine was said to cause cancer .

It does not but its excipients cause cancer .

Nizatidine has a near 100 bioavailability even when taken orally .

They help with stress ulcers and gastro – esophageal reflux duo to weakened sphincters . (lower HCl secretion = less refluxes) .

Cimetidine inhibits liver enzymes . Can stop drug metabolism and cause an increase in their toxicity .

Sheet # 12

Omeprazole (“ Hit & Run “ method of action) : Stops the pump . One dose decreases HCl for 24 hours . Even after it gone from the plasma .Taken once / day .

Very long biologic (not plasma) half-life .

Its biologic half-life > plasma half-life .

It does this by binding irreversibly to the pump .

New pumps must be made for H pumping .

Omeprazole is a pro-drug not a drug . It gets absorbed in the intestines . Low PH (acidity) can break it down in the stomach .

Therefore it is put in an enteric – coated tablet . It reaches the blood stream then heads to the parietal cells to work there .

Preparations

- **Lansoprazole**
- **Dexlansoprazole,**
- **Esomeprazole,**
- **Pantoprazole, and**
- **Rabeprazole.**

Omeprazole and lansoprazole are available over the counter for short-term treatment of GERD.

Indications:

1. Peptic ulcer
2. Stress ulcer
3. Drug of choice for Zollinger-Ellison syndrome?

   Gasrtin-producing tumor of the pancreas

3. GERD

Sheet # 13

Zollinger – Ellison Syndrome : Tumors (in abdomen and pancreas) called gastronomes secrete hormone gastrin which causes stomach (parietal cells) to produce too much acid .

Proton Inhibitors are the first choice here .

HCl in stomach has an important role : Calcium absorption .

Risk of proton pump inhibitor : X HCl = X Calcium absorption .

= fractures due to osteoporosis .

Proton-Pump Inhibitors

Adverse effects:

1. Diarrhea, colic, headache and diziness
2. Inhibit metabolism of warfarin, phenytoin
3. Prolonged inhibition of acid secretion ↑ risk of gastric neoplasia, low vit B12 and incomplete absorption of calcium carbonate products. An effective option would be to use calcium citrate as a source of calcium.
4. Increased risk of fractures of the hip, wrist, and spine (for one year or greater)
5. PPIs, particularly omeprazole, have been shown to decrease the effectiveness of clopidogrel due to inhibition of CYP2C19.