-Lecture 1: Drugs to treat peptic ulcer and GERD:

**NOTE: We'll talk firstly about the antimicrobial agents then we'll see the other agents:

➡Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment:

1-The triple therapy: Consists of:

A-PPI.

B-Amoxicillin (Metronidazole may be used in penicillin-allergic patients).

C-Clarithromycin.

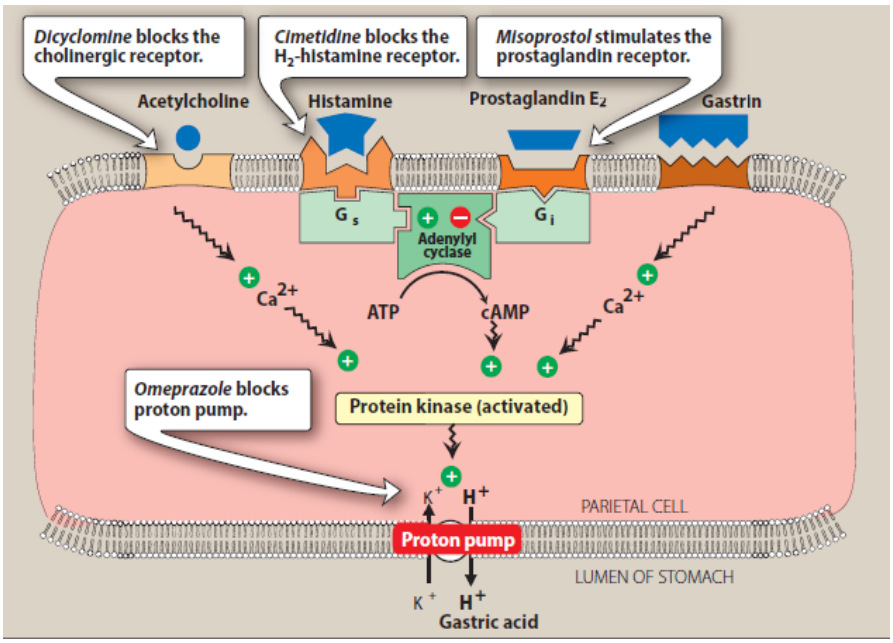
2-The quadruple therapy: Should be considered in areas with high resistance to Clarithromycin, and consists of:

A-Bismuth subsalicylate.

B-Metronidazole.

C-PPI.

D-Tetracycline.



The image on the right shows how each class regulates the secretion of gastric acid.

➡**NOW, let's talk about the other agents. See the next table in the next page:**

Class + name of the drugs	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
H2-receptor antagonists: Cimetidine, Ranitidine, Famotidine, Nizatidine.	-Blocks the binding of histamine to H2 receptors>>> reducing the secretion of gastric acid. -The histamine H2-receptor antagonists act selectively on H2 receptors in the stomach, but they have no effect on H1 receptors.	1-Peptic ulcers: Healing of duodenal and gastric ulcers. 2-Acute stress ulcer: Giver IV to prevent and manage acute stress ulcers associated with high-risk patients in ICU. 3-GERD	-Oral intake. -Distribute throughout the body including breast milk and the placenta. -Eliminated in urine. -Cimetidine, Ranitidine, and Famotidine are available in IV form.	-Cimetidine has endocrine effects because it acts as a nonsteroidal antiandrogen (Gynecomastia and Galactorrhea). -CNS effects in elderly after IV intake, -Cimetidine inhibits several CYP450 isoenzymes>>> interfere with the metabolism of other drugs (ex: Warfarin and Clopidogrel). -reduce the efficacy of drugs that require an acidic environment for absorption (ex: ketoconazole).
PPI: Dexlasnoprazole, Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole.	-They are prodrugs with an acid-resistant enteric coating to protect them from degradation by gastric acid>>> this coating is removed in duodenum and the prodrug is absorbed and transported to the parietal cell where it's converted to the active drug and forms a covalent bond with the H+/K+-ATPase enzyme.	1-Stress ulcer treatment and prophylaxis. 2-Treatment of GERD. -Erosive esophagitis. 4-Active duodenal ulcer. 5-Pathologic hypersecretory conditions (ex: Zollinger-Ellison syndrome). 6-Reduce the risk of bleeding from ulcers caused by Aspirin. 7-For NSAID-induced ulcer.	-Oral intake. -PPI should be taken 30-60 minutes before breakfast or the largest meal (See the notes below the table). -Esomeprazole, Lansoprazole, and Pantoprazole are available as IV forms. -Have a long duration of action due to covalent bonding with H+/K+-ATPase enzyme. -Eliminated in urine and feces.	-Omeprazole and Esomeprazole may decrease the effectiveness of Clopidogrel because they inhibit CYP2C19 and prevent the conversion of it to its active metabolite. -May increase the risk of fractures. -Low vitamin B12. -Impair the absorption of Calcium carbonate (See the notes). -Diarrhea and Clostridium difficile colitis. -Hypomagnesemia. -Increased incidence of pneumonia.
Prostaglandins: Misoprostol (prostaglandin E1 analog)	- Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect)	-Prevention of NSAID-induced gastric ulcer.	----------	-Diarrhea. -Nausea. -Contraindicated in pregnancy.

Antacids: Aluminum hydroxide, Magnesium hydroxide, Calcium carbonate.	- Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, palatability, and price. -The efficacy of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react).	-Symptomatic relief of peptic ulcer and GERD. -Promote healing duodenal ulcer. - Calcium carbonate preparations are also used as calcium supplements for the treatment of osteoporosis.	-Should be taken after meals for maximum effectiveness.	-Aluminum hydroxide causes constipation. -Magnesium hydroxide causes diarrhea.
Mucosal protective agents (aka: cytoprotective agents): Sucralfate and Bismuth subsalicylate.	-Sucralfate binds to positively charged groups in proteins of both normal and necrotic mucosa>>> forming complex gels with epithelial cells>>> creating a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal.	-Sucralfate: used for the treatment of duodenal ulcers and prevention of stress ulcers. -Bismuth subsalicylate: 1-Antimicrobial actions. 2-Inhibit the activity of Pepsin. 3-Increases secretion of mucus. 4-Interacts with glycoproteins in necrotic mucosal tissue to protect the ulcer.	----------	-Sucralfate interferes with the absorption of other drugs.

****Notes:**

➡ **Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than H2 antagonists do.**

➡ **An oral product containing Omeprazole combined with Sodium bicarbonate for faster absorption is also available over the counter and by prescription.**

➡ **If a once-daily PPI is only partially effective for GERD symptoms, increasing dosing to twice daily or administering the PPI in the morning and adding an H2 antagonist in the evening may improve symptom control and if an H2-receptor antagonist is needed, it should be taken well after the PPI.**

➡ **Calcium citrate is an effective option for calcium supplementation in patients on acid suppressive therapy, since absorption of the citrate salt is not affected by gastric pH.**

-Lecture 2: Drugs used to control chemotherapy-induced nausea and vomiting:

****Note: The next table shows the antiemetic drugs:**

Group +name of the drugs	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
Phenothiazines: Prochlorperazine.	-Blocks dopamine receptors.	-Effective against low or moderately emetogenic chemotherapeutic agents (ex: Fluorouracil and Doxorubicin).	----------	----------
5-HT3 receptor blockers: Ondansetron, Granisetron, Palonosetron, Dolasetron.	-Block 5-HT3 receptors in the periphery and the brain.	-Treat emesis linked with chemotherapy. -Ondansetron and Granisetron prevent emesis in 50-60% of cisplatin-treated patients. -Management of postoperative nausea and vomiting.	-Long duration of action. -Taken as a single dose prior to chemotherapy -Taken orally or IV. -Metabolized by the liver (See the notes). -Eliminated in urine.	-Electrocardiographic changes (ex: prolonged QTc interval) can occur with Dolasetron.
Substituted benzamides: Metoclopramide.	-Inhibition of dopamine in the CTZ.	-effective at high doses against the emetogenic cisplatin, preventing emesis in 30% to 40% of patients and reducing emesis in the majority of patients. -See the notes.	----------	-Antidopaminergic side effects (ex: extrapyramidal symptoms).
Butyrophenones: Droperidol and Haloperidol.	----------	-Moderate effective antiemetics. -Droperidol had been used most often for sedation in endoscopy and surgery, usually in combination with opioids or benzodiazepines. -High-dose haloperidol was found to be nearly as effective as high-	----------	-Droperidol may prolong the QTc interval.

		dose metoclopramide in preventing cisplatin-induced emesis.		
Benzodiazepines: Lorazepam and Alprazolam	----------	-Their beneficial effects may be due to their sedative, anxiolytic, and amnesic properties. -Useful in treating anticipatory vomiting.	----------	- Concomitant use of alcohol should be avoided due to additive CNS depressant effects.
Corticosteroids: Dexamethasone and Methylprednisolone.	-May involve blockade of prostaglandins.	-Effective against mildly to moderately emetogenic chemotherapy.	----------	----------
Substance P/neurokinin-1 receptor blocker: Aprepitant.	-Targets the neurokinin receptor in the brain>>> blocks the action of the natural substance.	-Indicated only for moderately or highly emetogenic chemotherapy regimens.	-Taken orally with Dexamethasone and a 5-HT3 antagonist. -Metabolized by CYP3A4.	-May affect the metabolism of other drugs that are metabolized by CYP3A4 (ex: Warfarin and oral contraceptives).

****Notes:**

➡ **As we said, 5-HT3 antagonists are extensively metabolized by the liver; however, only ondansetron requires dosage adjustments in hepatic insufficiency.**

➡ **Metoclopramide was previously used as a prokinetic drug for the treatment of GERD. However, due to the adverse effect profile and the availability of more effective drugs, such as PPIs, it should be reserved for patients with documented gastroparesis.**

****Combination therapy: Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity:**

1-Corticosteroids, most commonly Dexamethasone, increase antiemetic activity when given with high-dose Metoclopramide, a 5-HT3 antagonist, Phenothiazine, Butyrophenone, or a Benzodiazepine.

2-Antihistamines, such as Diphenhydramine, are often administered in combination with high-dose Metoclopramide to reduce extrapyramidal reactions or with Corticosteroids to counter Metoclopramide-induced diarrhea.

-Lecture 3: Antidiarrheals and Laxatives:

****Note: the next table shows the antidiarrheal drugs:**

Group + name of the drugs	Mechanism of action	Therapeutic uses	Adverse effects
Antimotility agents: Diphenoxylate and Loperamide.	-Activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis.	-Control diarrhea. -Analogs of Meperidine and have opioid-like actions. -At the usual doses, they lack analgesic effects.	-Toxic megacolon >>> so, they shouldn't be used in young children or in patients with severe colitis.
Adsorbents: Aluminum hydroxide and Methylcellulose.	-Act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa.	-Control diarrhea BUT less effective than the antimotility agents.	-Can interfere with the absorption of other drugs.
Agents that modify fluid and electrolyte transport: Bismuth subsalicylate.	-Its action may be due to its salicylate component as well as its coating action.	-For traveler's diarrhea>>> decreases fluid secretion in the bowel.	-Black tongue. -Black stools.

Now let's talk about the laxatives: the next table shows the laxatives:

Group + name of the drugs	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
Stimulants: 1-Senna.	-Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides.	-Causes evacuation of the bowels within 8-10 hours. -Causes water and electrolyte secretion into the bowel. -Treating opioid-induced constipation (when combined with Docusate containing stool softener).	-Oral intake.	----------
Stimulants: 2-Bisacodyl.	-Acts directly on nerve fibers in the mucosa of the colon.	-Potent stimulant of the colon.	-Available as suppositories and enteric-coated tablets.	----------
Irritant: Castor oil.	-Broken down in the small intestine to Ricinoleic acid.	- Ricinoleic acid is very irritating to the stomach and increases peristalsis.	----------	-Contraindicated in pregnancy because it causes uterine contractions.

Bulk laxatives: Hydrophilic colloids (indigestible parts of fruits and vegetables).	-Form gels in the large intestine>>> Causing water retention and intestinal distention>>> increasing peristaltic activity (similar actions produced by Methylcellulose, Psyllium seed, and bran.	----------	----------	-should be used cautiously in patients who are immobile because of their potential for causing Intestinal obstruction.
Saline: Magnesium citrate and Magnesium hydroxide.	-Non-absorbable salts that hold water in the intestine by osmosis. -Distends the bowel>>> increasing intestinal activity>>> producing defecation.	-Electrolyte solutions containing polyethylene glycol (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures.	----------	-A good point: PEG powder causes less cramping and gas than other laxatives.
Osmotic laxatives: Lactulose.	-Cannot be hydrolyzed by GI enzymes. -Oral doses reach the colon>>> degraded by the colonic bacteria into lactic, formic, and acetic acids >>> increases osmotic pressure>>> causing fluid accumulation, colon distention, soft stools, and defecation.	-Treatment of hepatic encephalopathy (due to its ability to reduce ammonia levels).	----------	----------
Stool softeners (surfactants): Docusate sodium and Docusate calcium	-Become emulsified with the stool>>> produce softer feces and ease passage.	-Often used for prophylaxis rather than acute treatment.	-May take days to become effective.	-Shouldn't be taken with Mineral oil because of the potential for absorption of Mineral oil
Lubricants: Mineral oil and Glycerin.	----------	-Facilitates the passage of hard stools	-Should be taken orally in upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.	----------
Chloride channel activators: Lubiprostone	-Activate chloride channels to increase fluid secretion in the intestinal lumen>>> eases the passage of stools and causes little change in the electrolyte balance.	-Used in the treatment of chronic constipation.	-Metabolism occurs quickly in the stomach and jejunum.	-Minimal drug-drug interactions.

-Lecture 4: Treatment for GI infectious diseases:

****We'll talk about treatment of 4 diseases, each in details:**

1-Viral Hepatitis: the next table shows the drugs for viral hepatitis:

Name of the drug	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
Interferons (α, β, γ).	-Appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.	- interferon-α-2b has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairy cell leukemia and Kaposi sarcoma.	-Not active orally. -May be taken intralesionally, subcutaneously, or IV -metabolized by the liver and kidney.	-Flu-like symptoms (ex: fever, chills, myalgias, and GI disturbances. -Fatigue and mental depression. -May potentiate myelosuppression caused by other bone marrow-suppressive agents. -See the notes.
Lamivudine (cytosine analog).	-Must be phosphorylated by host cellular enzymes to the triphosphate (active) form>>>inhibits HBV RNA-dependent DNA polymerase.	-Inhibitor of both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) reverse transcriptases (RTs).	-The intracellular half-life of the triphosphate is many hours longer than its plasma half-life. -Well absorbed orally -Widely distributed. -Excreted unchanged in the urine.	-Well tolerated. -Rare occurrences of headache and dizziness. -Dose reductions are necessary when there is moderate renal insufficiency.
Adefovir (Adefovir dipivoxil).	- Adefovir dipivoxil is a nucleotide analog that is phosphorylated by cellular kinases to Adefovir diphosphate, which is then incorporated into viral DNA>>>leads to termination of chain elongation and prevents replication of HBV.	----------	-Taken once a day. -Renally excreted via glomerular filtration and tubular secretion	-Nephrotoxicity may occur with chronic use. -Concurrent use with Tenofovir should be avoided. -Discontinuation of adefovir may result in severe exacerbation of hepatitis.
Entecavir (guanosine analog).	- Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral RT.	-Treatment of HBV infections. -Effective against lamivudine-resistant strains of HBV.	-Dosed once daily. -Excreted unchanged in the urine.	- Concomitant use of drugs with renal toxicity should be avoided.

Telbivudine (thymidine analog).	-Phosphorylated intracellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain.	-Treatment of HBV.	-Taken orally once a day. -Eliminated by glomerular filtration as the unchanged drug.	-Fatigue. -Headache. -Diarrhea. -Elevations in liver enzymes and creatine kinase.
Boceprevir and Telaprevir.	- These HCV NS3/4A serine protease inhibitors covalently bind to the NS3 protease active site, thus inhibiting viral replication in host cells.	-the first oral direct-acting antiviral agents for the adjunctive treatment of chronic HCV genotype 1.	- Boceprevir is taken with food to improve absorption. - The absorption of Telaprevir is enhanced when it is taken with non–low-fat food. -Metabolized by CYP450 isoenzymes. -Strong inhibitors of CYP3A4/5.	-Boceprevir causes anemia and dysgeusia. -Telaprevir causes rash, anemia, and anorectal discomfort.

****Notes:**

⟹**Chronic hepatitis B may be treated with:**

1-Peginterferon-α2a ⟹ taken subcutaneously once weekly.

2-Peginterferon-α2b ⟹ Taken intramuscularly or subcutaneously 3 times weekly.

3-Oral therapy ⟹ Lamivudine, Adefovir, Entecavir, Tenofovir, or Telbivudine.

⟹**Chronic hepatitis C may be treated with:**

-Combination of Peginterferon-α2a or Peginterferon-α2b + Ribavirin.

⟹**For genotype 1 chronic hepatitis C virus:**

-Protease inhibitor (ex: Boceprevir or Telaprevir) + pegylated interferon + Ribavirin.

⟹ **In "pegylated" formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either interferon-α-2a or -α-2b to increase the size of the molecule which delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.**

⟹ **The principal dose-limiting toxicities of Interferons are bone marrow suppression, severe fatigue and weight loss, neurotoxicity characterized by somnolence and behavioral**

disturbances, autoimmune disorders such as thyroiditis and, rarely, cardiovascular problems such as heart failure.

➡Boceprevir or Telaprevir should be used in combination with Peginterferon alfa and ribavirin in order to improve response rates and reduce the emergence of viral resistance.

2-Treatment of Leishmaniasis: The next table shows the drugs for Leishmaniasis:

Name of the drug	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
Sodium stibogluconate	-Isn't determined yet	-For Leishmaniasis.	-Not absorbed after oral intake. -Must be taken parenterally. -Distributed to the extravascular parts. -Eliminated in urine.	-Injection site pain. -Pancreatitis. -Elevated liver enzymes. -Arthralgias. -Myalgias. -GI upset. -Cardiac arrhythmia.
Miltefosine	-Appears to interfere with phospholipids in the parasitic cell membrane to induce apoptosis.	-Visceral leishmaniasis as well as cutaneous and mucocutaneous forms.	-First oral active drug for visceral leishmaniasis.	-Contraindicated in pregnancy.

3-Treatment of toxoplasmosis:

➡The treatment of choice is combination of Sulfadiazine and Pyrimethamine.

➡Leucovorin is commonly administered to protect against folate deficiency.

➡At the first appearance of a rash, Pyrimethamine should be discontinued, because hypersensitivity to this drug can be severe>>>Pyrimethamine with Clindamycin, or the combination of Trimethoprim and Sulfamethoxazole, are alternative treatments.

➡Trimethoprim/Sulfamethoxazole is used for prophylaxis against toxoplasmosis in immunocompromised patients.

4-Treatment of Giardiasis:

➡The treatment of choice is oral Metronidazole for 5 days.

➡An alternative treatment: Tinidazole which is taken orally as a single dose.

➡Nitazoxanide is also another treatment for giardiasis and is taken as a 3-day course of therapy.

➡Albendazole may be efficacious for giardiasis.

➡VERY IMPORTANT: Paromomycin is sometimes used for the treatment of giardiasis in pregnant patients.