Drugs Used in the Treatment of Gastrointestinal Diseases

Physiology of gastric Secretion

Parietal cells secrete 2 liters of acid/ day. Providing the optimal pH (between 1.8-3.5) for the function of the digestive enzyme pepsin. Stimulation of acid secretion involves translocation of H+/K+ ATPase to the apical membrane of parietal cell.

H+/K+-ATPase (proton pump) uses the energy derived from ATP hydrolysis to pump H+ into the lumen in **exchange** for potassium ions. Chloride and hydrogen ions are secreted **separately** from the cytoplasm of parietal cells and mixed in the canaliculi.

Stimulants of acid secretion:

1- **ACh** from enteric neurons stimulates the secretion of both hydrochloric acid (HCl) by parietal cells and pepsinogen by chief cells into the gastric lumen.
2- **Histamine** from ECL (enterochromaffin - like) cells.
3- **Gastrin** released by G cells.

Somatostatin in D cells inhibits acid secretion. When Gastric pH < 3, gastric D cells release somatostatin. It inhibits acid secretion by:

1- Direct effects on parietal cells.
2- Inhibiting release of histamine & gastrin.

Three phases in gastric acid secretion:

- **Cephalic Phase:** sight, smell, taste or thought of food, activate enteric neurons to release acetylcholine (ACh). Acetylcholine stimulates parietal, ECL, and G cells. In humans, the major effect of gastrin is indirect through the release of **histamine** from ECL cells not through direct parietal cell stimulation.

- **Gastric Phase:** Food **stretch** stomach walls activating a neural reflex to stimulate acid secretion. Peptides & amino acids in the food stimulate G cells to release gastrin which stimulate the ECL cells resulting in reduction of pH. Food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion..

- **Intestinal Phase:** Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer

A defect in the lining of the stomach or the duodenum. Causes of Peptic Ulcer:

- Helicobacter pylori (most common).
- Drugs such as aspirin & other NSAIDs.
- Other factors: Smoking, Stress or Alcohol.

Gastrinomas - Zollinger Ellison syndrome

A rare gastrin-secreting tumors. Gastrinomas are neuroendocrine tumors characterized by the secretion of gastrin with resultant excessive gastric acid production causing **severe peptic ulcer** disease and **diarrhea**, a combination referred to as the Zollinger- Ellison syndrome (ZES)

Symptoms of peptic ulcers

Burning pain in stomach between meals or at night, **bloating**, **heartburn**, **nausea** or **vomiting**. In severe cases, symptoms include: **Dark or black stool** (due to bleeding), **vomiting blood**, **weight loss** & severe **pain** in the mid to upper abdomen.

Complications of peptic ulcer

- Gastrointestinal bleeding (Sudden large bleeding can be life threatening).
- Cancer (Helicobacter pylori as the etiological factor)
- Perforation (hole in the wall) and penetration.

Treatment options for peptic ulcer:

- **Reduce** acid secretion (like H2 receptor antagonists)
- **Neutralize** acid in the lumen (antacids)
- **Protect** the mucosa from acid destruction (Sucralfate structures - physical barriers over ulcer)
- **Antibiotics** to eradicate Helicobacter pylori. If this is successful then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

Nonprescription remedies for treatment of heartburn & dyspepsia. Given 1 hour **after** a meal effectively neutralizes gastric acid for up to 2 hours.

$AL(OH)3 + HCl \rightarrow ALCl3 + H2O$

$2HCl + Mg(OH)2 \rightarrow MgCl2 + 2H2O$

- **Aluminum** antacids cause **constipation**, interfere with absorption of many drugs.
- **Magnesium** antacids have laxative action; **diarrhea**. Ionic magnesium stimulates gastric release (acid rebound)
- **Magnesium trisilicate** slow-acting antacid resulting in increase in the duration of action of the drug.
- Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation). Additionally, the combination reduces the required amount of aluminum hydroxide $Al(OH)_3$, thereby minimizing its interference with the absorption of other drugs.
    -
    - Both react slowly and without gas formation.
    - With both, metabolic alkalosis is uncommon.
    - Mg salts cause diarrhea.
    - Aluminum salts cause constipation.
    - Usually given in combination.
    - **Contraindicated in renal insufficiency** because they are excreted by the kidneys.

- **Calcium carbonate** associated with "acid rebound" with excessive chronic use, it may cause **milk-alkali syndrome** with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels so it should be used with caution, ensuring adherence to the recommended dose.

$2HCl + CaCO3 \rightarrow CaCl2 + CO2 + H2O$

- **Sodium bicarbonate**
  - Should be avoided as it counteracts diuretic therapy for **hypertension.**
  - Short duration of action, followed by acid rebound.
  - Highly absorbed, potentially causing **metabolic alkalosis**.
  - $CO2$ results in **belching**.

$NaHCO3 + HCl \rightarrow NaCl + H2O + CO2$

Under normal conditions, acetylcholine (ACh) and gastrin stimulate enterochromaffin-like (ECL) cells to release histamine. Histamine then binds to H_2 receptors on parietal cells, triggering a cAMP-mediated signaling cascade that activates the H^+/K^+-ATPase (proton pump), leading to hydrochloric acid (HCl) secretion into the gastric lumen.

When H_2 receptor antagonists are administered, they block histamine from binding to H_2 receptors, thereby:

- Preventing activation of adenylate cyclase
- Reducing cAMP production
- Inhibiting protein phosphorylation and proton pump activation

As a result, acid secretion is significantly reduced, even if ACh and gastrin are present.

H2- Receptor Antagonists (1970s-1990s)

Selective competitive inhibitors of the parietal cell H2 receptor on parietal cells and suppress basal and meal-stimulated acid secretion in a **dose dependent** manner. Also decrease volume of secretion and pepsin concentration. Were the most commonly prescribed drugs in the world, however these days PPIs are considered the alternative.

- **Cimetidine**, prototype, many problems.
- **Ranitidine**.
- **Famotidine**.
  50% first-pass metabolism, this decreases its bioavailability
- **Nizatidine**
  has little first-pass metabolism, this increases its bioavailability

When comparing H_2 receptor antagonists and proton pump inhibitors (PPIs):

- With H_2 receptor antagonists, acid secretion varies **(fluctuate)** throughout the day in response to meal timing and stimulation.
- In contrast, PPIs provide more consistent and sustained suppression of gastric acid production, maintaining a stable intragastric pH.

This is why PPIs are generally preferred over H_2 receptor antagonists for long-term acid suppression.

- Decrease secretion stimulated by: Histamine, Gastrin and Acetylcholine resulting at the end in decreased HCl production.
- Duration of action: 12 hours.
- Inhibit 60-70% of total 24-h acid secretion.
    - 90% of nocturnal acid **which** is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes.
    - 60% of day-time, meal stimulated, acid.

Clinical Uses:

- Gastroesophageal Reflux:
    - Under normal conditions, the lower esophageal sphincter (LES) remains closed, preventing the backflow of stomach acid into the esophagus. However, in certain pathological conditions where the LES becomes weakened or relaxed, acid can reflux into the esophagus, potentially leading to gastroesophageal reflux disease (GERD) and related complications
    - Prophylactically, before meals.
    - Afford healing for erosive esophgitis (which is the inflammation of the lining of the esophagus due to acid reflux) in less than 50% of patients.
    - Proton pump inhibitors are preferred.

- Non Ulcer Dyspepsia.
- Stress - Related Gastritis:
    - Can prevent bleeding, usually given IV.
- Peptic Ulcer Disease:
    - Replaced by PPI.
    - H2 – Receptor antagonists are not used for peptic ulcers, but if used, healing rate is greater than 80- 90% after 6-8 weeks which is considered a long time.
    - **NOT** effective in the presence of H. pylori infection.
    - **NOT** effective if NSAID is continued.

Adverse Effects:

- Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation.
- CNS: Confusion, hallucinations occur **only** with **IV** cimetidine to elderly patients in ICU.
- Endocrine Effects: Again only with IV cimetidine, can inhibit estradiole metabolism, and can increase prolactin serum levels causing infertility cases among women.
- Pregnancy and Nursing Mothers: Can cross placental barrier and appear in breast milk.
- Other Effects: Rarely can cause bradycardia and hypotension.

Drug Interactions

- Cimetidine can **inhibit** cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6, and **CYP3A4**), so can increase half life of many drugs metabolized by cytochrome P450, so we need to reconsider the dose of these drugs.
- Ranitidine binds 4-10 times less.
- Nizatidine and Famotidine binding is negligible.

Proton Pump Inhibitors

PPI(1990s) are available under various brand names and are produced by multiple pharmaceutical companies in the market. They are very efficacious and safe drugs.

- Omeprazole (oral).
- Rabeprazole (oral).
- Lanzoprazole (oral and IV).
- Pantoprazole (oral and IV).
- Esmoprazole (oral and IV).
    - They are formulated as a prodrug which is released in the intestine.
    - Less common formulas are the Immediate Release Suspension results in rapid response.

PPIs vs. H_2 Receptor Antagonists

- H_2 receptor antagonists block histamine from binding to H_2 receptors on parietal cells, reducing cAMP production and downstream activation of acid secretion.
- Proton pump inhibitors (PPIs) directly inhibit the H^+/K^+-ATPase (proton pump), blocking the final step of acid secretion and leading to a more profound and sustained reduction in gastric acidity.

Pharmacokinetics

- They are lipophilic weak bases (pKa 4-5).
- After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus.
- The prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells.
- There, it undergoes a molecular conversion to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.
- Rabeprazole has immediate release, Omeprazole have faster onsets of action.
- Should be given one hour before meal. Although they have short half lives, their effect lasts for 24 hours due to **irreversible** inhibition so they are given once daily.

Pharmacodynamics

Inhibit both fasting and meal-stimulated secretion because they block the **final** common pathway of acid secretion (90-98% of 24-hour secretion).

Clinical Uses

- Gastroesophageal Reflux (GERD):
    - They are the most effective agents in all forms of GERD and complications.
- Nonulcer Dyspepsia:
    - Modest activity.
    - 10-20% more beneficial than a placebo.
- Stress-Related Gastritis:
    - Oral immediate release omeprazole administered by **nasogastric tube**.
    - For patients **without** a nasoenteric tube, **IV** H2-antagonists are preferred because of their proven efficacy.
    - All cases of stress related conditions could be treated effectively with PPI.
- Gastrinoma and other Hypersecretory Conditions: Usually **high doses** of omeprazole are used.

- Peptic Ulcer Disease:
  - They heal more than 90% of cases within **4-6 weeks.**
  - H.pylori - associated ulcers:
    In addition to reducing acidity, PPI eradicate H.pylori by direct antimicrobial activity and by lowering MIC of the antibiotics.
  - Triple Therapy:
    - **PPI** twice daily.
    - **Clarithromycin** 500mg twice daily.
    - **Amoxicillin** 1gm twice daily ,OR, **Metronidazole** 500mg twice daily.
  - NSAID-associated ulcers:
    - PPIs promote ulcer healing **despite continued** NSAID use.
    - Also used to **prevent** ulcer **complications** of NSAIDs.
  - Rebleeding peptic ulcer:
    - Oral or IV.
    - High pH may enhance coagulation and platelet aggregation.

Adverse Effects

- General: Diarrhea, headache, abdominal pain, NOT teratogenic in animals, but NOT used in pregnancy.
- Reduction of **cyanocobalamine** (vitamin B12) absorption.
- Increased risk of GI and pulmonary infection as a result of vitamin B12 malabsorption (Vitamin B12 can help balance immune responses to better fight viral and bacterial infections), so vitamin B12 supplements should be given from time to time.
- Increased serum gastrin levels:
  - Hyperplasia of ECL cells.
  - Carcinoid tumors in rats (NOT proven in humans).
  - Increase proliferative rate of colonic mucosa (RARE).
- Chronic inflammation in gastric body.
- Atrophic gastritis and intestinal metaplasia. (Gastritis is a general term for a group of conditions with one thing in common: Inflammation of the lining of the stomach. A change of cells to a form that does not normally occur in the tissue in which it is found)

Drug Interactions:

- May affect absorption of drugs due to **decreased** gastric acidity like **digoxin** and **ketoconazole**.
- Omeprazole can inhibit metabolism of drugs such as **diazepam** and **phenytoin**.
- **Rabeprazole** and **pantoprazole** have NO significant interaction being the drugs of choice for patients needing to take other drugs.

Drugs Affecting GI Motility

- Laxative Agents (in cases of constipation).
- Antidiarrheal Agents.

Laxatives

Before using laxatives, these Nonpharmacologic Remedies should be considered first:

- High fiber diet.
- Adequate fluid intake.
- Regular exercise.
- Responding to nature's call.

Laxatives Bulk-Forming Laxatives: Are indigestible, hydrophilic colloids that **absorb water**, forming a bulky, emollient gel that distends the colon and **promotes peristalsis**. Can cause bloating and flatus.

- Natural Plant Products:
  - Psyllium.
  - Sterculia "Normacol"
  - Methylcellulose.
- Synthetic Fibers:
  - Polycarbophil.

Stool Surfactant Agents (Softeners): They permit water and lipids to penetrate and soften the stool. Given orally or rectally.

- Docusate.
- Glycerin suppository (the most famous).
- Mineral oil:
  - Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.
  - Used to prevent and treat **fecal impaction**.
  - Aspiration can cause **lipoid pneumonia** (Aspiration pneumonia occurs when food or liquid is breathed into the airways or lungs, instead of being swallowed).
  - Can impair absorption of fat-soluble vitamins so vitamin supplements should be taken.

Osmotic Laxatives (Purgatives): Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- Magnesium oxide (Milk of Magnesia):
  - Can cause hypermagnesemia.
  - Large doses of magnesium citrate and sodium phosphate can cause **Purgation** which is rapid bowel evacuation within (1-3) hours. This might cause volume depletion.
- Sorbitol.
- Lactulose.
  - Sugars metabolized by bacteria producing severe flatus and cramps.
- Balanced Polyethylene Glycol:
  - Safe solution: no intrvascular fluid or electrolyte shifts. Does not cause cramps or flatus.
  - Used for complete colonic cleansing before endoscopy.
  - PEG is an inert, nonabsorbable, osmotically active sugar.
  - Sodium sulfate, chloride, bicarbonate and potassium chloride.
  - For colonic cleansing, it should be ingested rapidly (4L over 2-4hs).
  - For chronic constipation, PEG powder is mixed with water or juice.

Stimulant Laxatives (Cathartics):

- ✓ Direct stimulation of the enteric system.
- ✓ Colonic electrolyte and fluid secretion.
- ✓ Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.

- ✓ May be needed in neurologically impaired patients and in bed- bound patients in long term care facilities.

- Anthraquinone Derivatives:
  - Aloe.
  - Senna.
  - Cascara
    - Poorly absorbed
    - After hydrolysis, produce bowel movement in (6-12) hours.
    - Cause brown pigmentation of the colon" Melanosis Coli".
    - Not carcinogenic.
- Castor Oil:
  - Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant.
  - Was used as purgative to clean the colon before procedures.

Normal situation

1- Gut distention stimulates 5-HT release from EC cells.
2- Stimulation of 5-HT3 receptors on the extrinsic afferent nerves stimulate nausea, vomiting, or abdominal pain.
3- 5-HT also stimulates 5-HT1P receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for peristaltic and secretory reflex activity.
4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of ACh & calcitonin gene related peptide (CGRP), promoting reflex activity.

Tegaseroid:

Is a serotonin 5-HT4 partial agonist, which are presynaptic receptors of the submucosal intrinsic primary afferent nerves which enhance the release of their neurotransmitters.

These neurones stimulate proximal bowel contraction (via ACh and substance P) and distal relaxation (via nitric oxide and VIP).

The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility. Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity.

Clinical Uses

- Chronic constipation.
- Nonulcer dyspepsia.
- Gastroparesis.
- Irritable bowel syndrome.

Adverse Effects

- Extremely safe drug.
- Diarrhea occurs in 9% of patients but resolves within days.
- Expensive.

Antidiarrheal Agents

Can be used in mild to moderate acute diarrhea. Should **NOT** be used in the presence of infective diarrhea. Can be used to control chronic diarrhea, like in irritable bowel syndrome or inflammatory bowel disease.

Opioid Agonists:

- Have significant constipating effects:
  - Inhibit presynaptic cholinergic nerves, leading to increased colonic transit time and increased fecal water absorption.
  - Decrease mass colonic movements and gastrocolic reflex.
- Can have CNS effects and addiction potential.
- Usually combined with atropine to reduce dependence.

Loperamide: Does not cross BBB. Has NO analgesic or addiction potential.

Diphenoxylate: Can have CNS effects and dependence.

Kaolin and Pectin:

- Kaolin is a naturally occurring hydrated magnesium silicate.
- Pectin is an indigestible carbohydrate derived from apples.

They should be taken far from other medications. Both act to absorb bacteria, toxins and fluid. Usually combined, e.g. Kaopectate.

Bile salt-binding resins:

- *Cholestyramine*
- *Colistipol.*

Malabsorption of bile salts (e. g .after surgical resection), can cause diarrhea. These drugs can bind bile salts. Can cause bloating, flatulence, constipation and fecal impaction. Also, drug and fat malabsorption.

Octreotide:

Is a synthetic octapeptide with actions similar to somatostatin. *Somatostatin* is a 14 amino acid peptide released in the GIT and pancreas as well as from the hypothalamus:

1. Inhibits release of many hormones.
2. Reduces intestinal fluid and pancreatic secretions.
3. Slows GIT motility and gallbladder contraction.
4. Contracts blood vessels.
5. Inhibits secretion of some anterior pituitary hormones.

Clinical Uses

1. Inhibition of endocrine tumor effects: Carcinoid can cause secretory diarrhea and systemic symptoms like flushing and wheezing.
2. Diarrhea due to vagotomy or dumping syndrome or and AIDS.

3. In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.
4. pituitary tumors and GI bleeding.

Vagotomy usually means cutting the branch of the vagus nerve that tells your stomach to secrete gastric acid

Dumping syndrome is a condition in which food, especially food high in sugar, moves from your stomach into your small bowel too quickly after you eat

Scleroderma is an uncommon condition that results in hard, thickened areas of skin

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Drugs Used in the Treatment of Irritable Bowel Syndrome

IBS is an idiopathic chronic, relapsing disorder characterized by: Abdominal discomfort, *pain, bloating, distention, or cramps* with alterations in bowel habits, *diarrhea, constipation, or both.* Pharmacologic therapies for IBS are directed at relieving abdominal pain and discomfort and improving bowel function.

Antispasmodic or Anticholinergic Agents:

- *Dicyclomine*
- *Hyoscyamine.*

They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle. At usual low doses, have minimal side effects.

Spasm is not an important symptom in IBS.

Serotonin 5-HT3- Receptor *Antagonists*:

- *Alosterone*
    - 5-HT3 receptors are present in the afferent pain fibers in the extrinsic sensory neurons. Also present on the terminals of the enteric cholinergic neurons. Centrally, 5-HT3 is involved in the central response to visceral afferent stimulation.
    - Selective antagonist of 5-HT3 (the prof. suggested adding 5-HT4 but I think this is not accurate) receptors.
    - Has long duration of action.
    - Approved for women with severe IBS in whom **diarrhea** is the prominent symptom.
    - Efficacy in men is not established.
    - Can cause ischemic colitis (Ischemic colitis occurs when blood flow to part of the large intestine is temporarily reduced) severe constipation requiring hospitalization and surgery.

Serotonin 5-HT 3 Receptor *Agonists*: (It is actually 5-HT**4** agonist, but that's what is written in the slides)

- *Tagaserod*
    - Approved for short term treatment of women with IBS who predominantly have **constipation** (causing less severe side effects compared to other drugs mentioned).
    - Reduces pain, bloating and hardness of stool
    - Expensive.

Diagnosis of irritable bowel syndrome (IBS) begins with symptomatic treatment, focusing on controlling symptoms and addressing stress, which may be the contributing factor. Patient education is essential.

The next step is to identify the most prominent symptom. If constipation is predominant, the patient should be advised to increase dietary fiber and fluid intake. If diarrhea is the main symptom, the patient should be counseled to follow a lactose-free, caffeine-free diet and avoid foods and drugs that can trigger diarrhea.

Since some patients may experience both constipation and diarrhea, they should be educated on how to adjust their diet accordingly when symptoms fluctuate.

If dietary changes fail to relieve constipation, bulk-forming laxatives may be used, along with antispasmodic agents if necessary. If these are ineffective, serotonin 5-HT_4 agonists like tegaserod can be considered.

If diarrhea does not improve with diet modifications, loperamide or other antispasmodics may be used, and serotonin 5-HT_3 antagonists such as alosetron may be added.

In both types, psychotherapeutic behavior modification, stress reduction, and possibly antidepressants for associated pain can be beneficial, especially since stress is often a core factor in IBS. However, these measures should be considered as a last resort.

Antiemetic Agents

Nausea and vomiting may be manifestations of a wide variety of conditions which are important in determining the treatment, including:

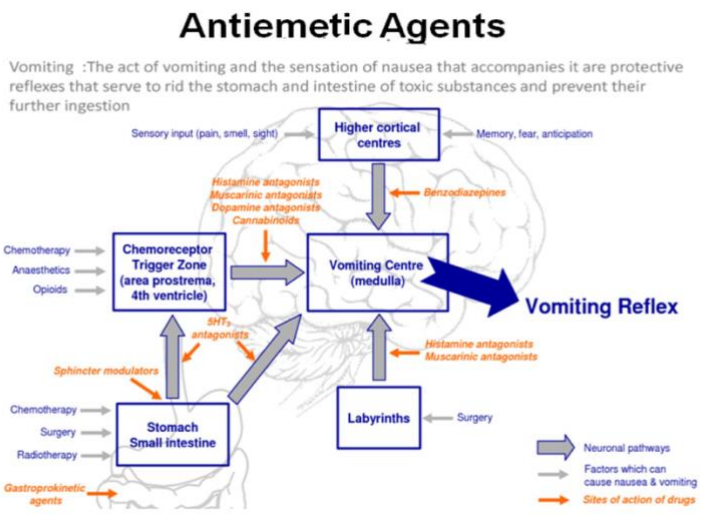
- Adverse effects of medications.
- Systemic disorders or infections and Pregnancy.
- Vestibular dysfunction.
- CNS infection or increased pressure and Peritonitis.
- Hepatobiliary disorders.
- Radiation or chemotherapy.
- GIT obstruction, dysmotility, or infections.

Pathophysiology: The brainstem "**vomiting center**" coordinates vomiting through interactions with cranial nerves **VIII** and **X** and neural networks in the nucleus tractus solitarius that control respiratory, salivatory, and vasomotor Centers.

Vomiting center contains high concentrations of: (determining the center is part of the treatment)

- M1 receptors.
- H1 receptors.
- Neurokinin 1 (NK1) receptors.
- 5-HT3 receptors.

PLEASE SEE THE DIAGRAM.



Serotonin 5-HT3 Antagonists

- *Ondansetron*
- *Granisetron*

Block **central** 5-HT3 and **peripheral** (main effect) 5-HT3 receptors. This results in preventing emesis due to vagal stimulation and chemotherapy. Other emetic stimuli such as **motion sickness** are **poorly** controlled.

Uses: Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting. **Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist.**

Adverse effects: Headache, dizziness, and constipation.

Neurokinin 1 Receptor (NK1) Antagonists : Block central NK1 receptors in the area postrema.

- *Aprepitant*

Used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy.

Cannabinoids

- *Dronabinol*
- *Nabilone*

Psychoactive agents (so their adverse effects are related to psychological view). Used for chemotherapy-induced vomiting. Mechanisms for these effects are not understood.

Adverse effects: Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.

Antipsychotic drugs:

- *Prochlorperazine*
- *Promethazine*
- *Droperidol*

Antiemetics due to blocking dopamine and muscarinic receptors and **Sedative** effects due to antihistamine activity.

Benzodiazepines: Reduce vomiting caused by **anxiety**

- *Lorazepam*
- *Diazepam*

Antiprotozoal drugs

Protozoal and helminthic infections are a major cause of disease in many parts of the world. Some of these diseases in **migrant** workers or **individuals** returning from an endemic area.

Selected PROTOZOAL DISEASES

Amebiasis

The protozoan Entamoeba histolytica causes amebiasis, an infection that is endemic in parts of the United States. The parasite can be present in the host as either an **encysted** (which is passed in feces, resistant to treatment and infective) or a **trophozoite form** (active, feeding, motile, can replicate and can be encysted).

Initial ingestion of the cyst may result either in **no** symptoms or in **severe** amebic dysentery characterized by the frequent passage of bloodstained stools. Symptom occurs after **invasion** of the intestinal mucosa by the actively motile and phagocytic **trophozoite form** of the protozoan.

- Trophozoites may spread to the liver through the portal vein and produce acute **amebic hepatitis**.
- Many patients continue to excrete cysts for several years after recovery from the acute disease and therefore are a hazard to themselves and other persons.

This organism can cause:

- **Asymptomatic** intestinal infection.
- Mild to moderate **colitis** (most prominent that's what the prof. said)
- Severe intestinal infection (dysentery).
- **Ameboma** (a tumor-like mass (not real tumor) in the intestines in amebiasis which results in a large local lesion of the bowel).
- Liver abscess and other extraintestinal infection

Treatment of Specific Forms of Amebiasis

Asymptomatic Intestinal Infection: Asymptomatic carriers are treated with a luminal amebicide. **Standard luminal amebicides** are: *Diloxanide furoate, Iodoquinol, and Paromomycin.* Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis.

Amebic Colitis (mild to moderate form of amebiasis)

- *Metronidazole* + *a luminal amebicide* is the treatment of choice.
- *Tetracyclines* and *erythromycin* are **alternative** drugs for moderate colitis but are NOT effective against extraintestinal disease.
- *Dehydroemetine or emetine* can also be used, but are best **avoided** because of toxicity.

Balantidium coli

The largest of the protozoans that infect humans. Trophozoite form is covered with cilia, which impart mobility. Infection is acquired through the ingestion of cyst-contaminated soil, food, or water.

The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine. Healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea. Nutritionally stressed patients may develop severe dysentery.

Classes of oral antiprotozoal drugs

Commonly used oral antiprotozoal drugs can be generally classified into two main groups:

- *Antimalarial drugs*
- *Miscellaneous antiprotozoals.*

In addition to their use as antiprotozoals, some of them such as metronidazole and doxycycline are also used for treating bacterial infections.

Miscellaneous antiprotozoals: Commonly used miscellaneous antiprotozoals include:

- *metronidazole*
- *tinidazole*
- *nifuratel.*

Metronidazole

Drug of choice in the treatment of extraluminal amebiasis. It kills trophozoites but not cysts of E. histolytica and effectively eradicates intestinal & extraintestinal tissue infections. Metronidazole (Flagyl, Metrogel) exerts activity against most anaerobic bacteria and several protozoa.

The drug freely penetrates **protozoal** and **bacterial** cells but NOT mammalian cells (due to) The enzyme, pyruvate-ferredoxin oxidoreductase, found only in **anaerobic** organisms, reduces metronidazole and thereby activates the drug. Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

- **Clinical Uses (Amebiasis): Metronidazole** The drug of choice in the treatment of all tissue infections with E histolytica (treating hepatic abscess; intestinal wall/ extraintestinal infections)
  NOT effective against **luminal** parasites and so must be used with a luminal amebicide to ensure eradication of the infection (because it kills trophozoites but not cysts)
- **Clinical Uses (Giardiasis): Metronidazole** is the treatment of choice. Efficacy after a single treatment is about 90% (Tinidazole is equally effective).
- **Clinical Uses (Trichomoniasis): Metronidazole** is the treatment of choice. A single dose of 2 g is effective.

Adverse Effects & Cautions

- Common: Nausea, headache, dry mouth, metallic taste.
- Infrequent adverse effects: Vomiting, diarrhea, insomnia (when affecting the CNS), weakness, dizziness,.
- Rare: Pancreatitis and severe central nervous system toxicity (Here, Tinidazole is better tolerated).

Metronidazole is best avoided in **pregnant** or **nursing** women, although congenital abnormalities have not clearly been associated with use in humans.

Tinidazole: Similar activity, but better toxicity profile than metronidazole, so it is best suited for more complicated cases.

Tinidazole works as well as metronidazole and has many of the same side effects (with the exception of CNS effects, which are typically better tolerated with Tinidazole) , but it can be given in a single dose.

Nifuratel: Nifuratel can be used as an alternative to metronidazole or tinidazole in the treatment of trichomoniasis.

Antimalarial Drugs

Malaria is a mosquito-borne infectious disease of **humans** and other **animals** caused by parasitic **protozoans** (a group of single-celled microorganism) belonging to the genus **Plasmodium**.

Life Cycle of Malaria Parasites

- Malaria transmitted by the bite of infected female called the **Anopheline** mosquitoes.
- From the mosquito salivary glands enter the circulation then localize in hepatocytes to multiply, and develop
- Asymptomatic for 5 to 15 days, depending on the Plasmodium.
- Tissue schizonts rupture, releasing thousands of merozoites that enter the circulation, invade erythrocytes where mature schizonts form.
- Schizont-containing erythrocytes rupture, each releasing 6 to 32 merozoites. This process produces **febrile attacks**.

Chloroquine: Most useful agent to terminate an acute attack. It is available as oral, IV, and IM preparations depending on the patient's condition. Resistance may develop, therefore, it should be given under medical supervision. Can commonly cause nausea, headache, and is **teratogenic** therefore, it is contraindicated in pregnancy except in severe cases where the mother's condition takes priority over fetal safety.

Quinine: Oldest drug, from Cinchona tree. Has many actions, but considered to be toxic. It is still used, with no resistance to its action

Artemisinin: New drug, from **Sweet wormwood** (الشيح)

Doxycycline: it is an antibiotic that also has an effective action against malaria; however, its use must consider the potential for bacterial resistance.

Pyrimethamine

Anthelmintics

Infection by helminths (worms) may be limited solely to the intestinal lumen or may involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue other that intestinal tract.

Helminths have either a simple cycle of egg deposition and development of the egg to produce a mature worm, **OR** others must progress through one or more hosts and one or more morphological stages, each metabolically distinct from the other, before emerging as an adult.

Pathogenic helminths can be divided into the following:

- Cestodes (flatworms)
- Nematodes (roundworms)
- Trematodes (flukes)
- Acanthocephala (thorny- headed worms)

CESTODES

- Flat worm, tape-like, Segmented parasites.
- Length range from mm to meters.
- Scolex (Head) provided with suckers, Hooks +/- (attachment)
- Adult worms are in Gastrointestinal tract
- Digestive tract is absent, absorb nutrients from body wall
- Another stage are the Hermophrodites (Reproductive system, Excretory & Nervous systems present)
- Complete chain of segments known as **strobila**, Segment - Proglottid
- Life span - 5 to 25 years

NEMATODE the roundworms: The body of a nematode is long and narrow, resembling a **tiny thread** in many cases, and this is the origin of the group's name**.** Most living roundworms are **microscopic**. On the other hand, one species of parasitic nematode can reach 13 meters in length

TREMATODES الديدان المثقوبة

Trematode infections occur **worldwide**. Trematodes, also called **flukes**, cause various clinical infections in humans. The parasites are so named because of their **conspicuous suckers**, the organs of attachment.

ACANTHOCEPHALA مشوكات الرأس

Thorny-headed worms, are parasites that live in the gut of vertebrates and - earlier in their life cycle - within invertebrates. Acanthocephalans lack a mouth or alimentary canal. Adult stages live in the intestines of their host and uptake nutrients which have been digested by the host, directly, through their body surface.

Anthelmintics: Are drugs that act either **locally** to expel worms from the gastrointestinal tract or **systemically** to eradicate adult helminths or developmental forms that invade organs and tissues

Most available anthelmintic drugs exert their antiparasitic effects by interference with:

(1) Energy metabolism (2) Neuromuscular coordination (3) Microtubular function (4) Cellular permeability

TREATMENT FOR INFECTIONS CAUSED BY *NEMATODES*

Piperazine

- Prolonged treatment and might need a **purgative** to help expel the worms from the body.
- Piperazine (Vermizine) contains a heterocyclic ring that lacks a carboxyl group which may influence its pharmacological activity.
- Piperazine acts as an **agonist** at gated chloride channels on the parasite muscle.
- Piperazine acts on the musculature of the helminths to cause **reversible** flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. This results in expulsion of the worm.

Diethylcarbamazine

It interferes with the metabolism of **arachidonic** acid and **blocks** the production of **prostaglandins**, resulting in capillary **vasoconstriction** and impairment of the passage of the microfilaria.

Mebendazole"Vermox":

- Widely **used**, **wide (broad) spectrum**, **safe** drug.
- Threadworm: Enterobius vermicularis, simple teatment: **single** dose, can be repeated after 3 weeks.
- Hockworm: Ankylostomiasis: 2 tablets * 3 days.
- Roundworm: Ascaris lumbricoidis

TREATMENT FOR INFECTIONS CAUSED BY *CESTODES*

Niclosamide: Niclosamide is amchlorinated salicylamide that inhibits the production of energy derived from anaerobic metabolism. Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite. The drug affects the **scolex** and **proximal segments** of the cestodes, resulting in **detachment** of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel.

TREATMENT FOR INFECTIONS CAUSED BY *TREMATODES*

Praziquantel: The neuromuscular effects of praziquantel (Biltricide) appear to increase parasite motility leading to spastic paralysis. The drug increases calcium permeability through parasite-specific ion channels, so that the muscle cells of the parasite accumulate calcium

This action is followed by exposure of hitherto masked tegmental antigens, lipid anchored protein, and actin. Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault.

Antiviral Agents

Viruses are obligate intracellular microbes that use many of the host cell's biochemical mechanisms and products to sustain their viability. A mature virus (virion) can exist outside a host cell and still retain its infective properties.

The virus must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles

Classification of Viruses

Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid). Many viruses possess an outer envelope of protein or lipoprotein. Viral cores can contain either DNA or RNA so viruses may be classified as DNA viruses or RNA viruses. Further classification is usually based on morphology, cellular site of viral multiplication, or other characteristics.

DNA viruses

- Adenoviruses (colds, conjunctivitis)
- Hepadnaviruses (hepatitis B)
- Herpesviruses (cytomegalovirus chickenpox)
- Papillomaviruses (warts)

RNA viruses

- Arborviruses (yellow fever)
- Arenaviruses (meningitis)
- Orthomyxoviruses(influenza)
- Paramyxoviruses (measles, mumps)
- Picornaviruses (meningitis, colds)
- Rubella virus (German measles)
- Retroviruses (AIDS).

Viruses live intracellular, so drugs should be able to enter the human cells.The most encountered viral infections of the GI tract are :

Cytomegalovirus (CMV)

- CMV is a highly prevalent infection globally and is capable of producing severe systemic disease mostly in neonates, elderly and immunocompromised patients.
  However, immunocompetent patients can also be affected with much less complications.
- CMV involvement of the GI tract is the most common manifestation of an active CMV infection.
- Primary CMV infection often cause an asymptomatic syndrome.
- CMV can remain latent in the macrophages after the primary infection, leading to reactivation at a later time.

Herpes simplex virus (HSV)

- HSV most commonly involve the esophagus and the anorectal region; however it can cause infections throughout the GI tract.
- Although most immunocompetent patients have self- limited disease, immunocompromised patients are at risk of disseminated infection.
- Patients with HSV esophagitis often present with acute onset nausea and vomiting, chest pain and less commonly GI bleeding.
- Immunocompromised patients are at risk of severe complications such as esophageal **perforation**.

Adenovirus

- Enteric Adenovirus types 40 and 41 is transmitted through fecal oral route and primarily affects infants and young children.
- Severe adenovirus infection with high mortality rate can affect immunocompromised patients or transplant recipients.
- Patients often present with watery diarrhea lasting 5–12 days.
- Adenovirus can cause lymphoid hyperplasia leading to obstruction particularly in the pediatric population. In such cases, hospitalization is required for close monitoring and supportive therapy.

Gastroenteritis Caused by Rotaviruses

Rotaviruses are double-stranded RNA viruses in the family Reoviridae. They are responsible for common diarrheal illness which can particularly affect pediatric and elderly patients, although prevention through vaccination is becoming more common. The virus is primarily spread by the fecal-oral route

These viruses are widespread in children, especially in day-care centers. The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.

Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection or, if they do, are asymptomatic.

The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age, so infections can spread through nursing homes and similar facilities. In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease. The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

Infected individuals exhibit fever, vomiting, and diarrhea. The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi. Infection can cause food intolerance, especially with respect to lactose.

The illness generally appears after an **incubation** period of about **two days** and lasts for approximately **one week** (three to eight days). Without **supportive treatment**, the illness can cause severe fluid loss, dehydration, and even death.

Even with milder illness, repeated infections can potentially lead to **malnutrition**, especially in developing countries, where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water. Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their **risk of death** from rotavirus infection.

Diagnosis

- The most common clinical tool for diagnosis is **enzyme immunoassay**, which detects the virus from **fecal** samples.
- **Latex agglutination assays** are also used. Additionally, the virus can be detected using electron microscopy and **(RT- PCR** which is the best tool)**.**

Treatment

- **Supportive** with oral **rehydration** therapy.
- Preventive **vaccination** is also available.
    - In the United States, rotavirus vaccines are part of the standard vaccine schedule and administration follows the guidelines of the World Health Organization (WHO).
    - The WHO recommends that all infants worldwide receive the rotavirus vaccine, the first dose between six and 15 weeks of age and the second before 32 weeks.

Gastroenteritis Caused by Noroviruses

Noroviruses, commonly identified as Norwalk viruses, are **caliciviruses**. Several strains can cause gastroenteritis. There are millions of cases a year, predominately in infants, young children, and the elderly. These viruses are easily transmitted and highly **contagious** (even more than Rotavirus). They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships.

The viruses can be transmitted through **direct** contact, through touching contaminated surfaces, and through contaminated food. Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.

The signs and symptoms of norovirus infection are similar to those for rotavirus, with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting.

The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur, so supportive treatment may be needed.

Norovirus can be detected using PCR or enzyme immunoassay (EIA) testing. **RT-qPCR** is the preferred approach as EIA is insufficiently **sensitive**. If EIA is used for rapid testing, diagnosis should be confirmed using PCR.

No medications are available, but the illness is usually self-limiting. **Rehydration** therapy and **electrolyte replacement** may be used. Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Vaccine
Norovirus gastroenteritis	Noroviruses	Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days	Highly contagious via direct contact or contact with contaminated food or fomites	Rapid enzyme immunoassay confirmed with RT-qPCR	None
Rotavirus gastroenteritis	Rotaviruses	Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death	Fecal-oral route; children and elderly most susceptible	Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR	Preventive vaccine is recommended for infants

Please let me know if there is anything missing.

سبحان الله و بحمده عدد خلقه و رضا نفسه و زنة عرشه و مداد كلماته

النسخة المعدّلة :

- **(Page 3): Nizatidine** has little first-pass metabolism, this increases its bioavailability (increases instead of decreases)
- Some punctuation marks were missing or misused and have been corrected (not related to the content).
- Please note that the images from the professor's slides are not included in this sheet. If you'd like, you can see them from the slides.