Pharmacology

Second Year Students
UJ-GIG GI Booklet

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The University of Jordan
Gastroenterology Interest Group (UJ-GIG)
Booklet

Pharmacology

Peptic Ulcer treatment

Written by: Nour Alhaj Qassim

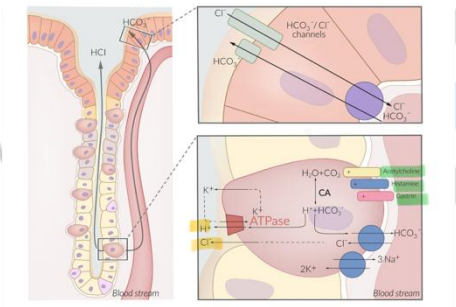
Edited by: Rawan Fratekh

[Outlines]

1) **Review: physiology of gastric secretion**
2) **Review: peptic ulcer disease**
3) **Treatment options:**
   - **Neutralization of acid (Antacids)**
   - **H2 receptor antagonist**
   - **Proton pump inhibitors, PPI**

[Review: physiology of gastric secretion]

- Parietal cells secrete 2 liters of acid/day, a huge amount that aids in digestion.
- Optimal pH (between 1.8 and 3.5) for the function of the digestive enzyme pepsin.
- Stimulation of acid secretion from the parietal cells involves the translocation of H+/K+-ATPase to the apical membrane of the parietal cell.
- H+/K+-ATPase (proton pump) uses the energy derived from ATP hydrolysis to **pump H+ into the lumen of the stomach in exchange for potassium ions**.
- Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi (lumen).



Gastric acid secretion

Gastric acid (HCl) is secreted by the parietal cells of the gastric glands, which is stimulated by histamine, ACh, and gastrin. Cytoplasmic carbonic anhydrase converts CO_2 and H_2O into H^+ and HCO_3^-. Intracellular HCO_3^- is exchanged for Cl^- through the basolateral membrane. The H^+/K^+-ATPase pumps on the apical cell membrane of parietal cells secrete H^+ ions into the lumen. H^+ and Cl^- are secreted into the gastric lumen as HCl. HCO_3^- is secreted into the gastric lumen in exchange for Cl^- by the mucous neck cells of the gastric glands.

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➔ **Stimulants of acid secretion:**

1) **Ach** from enteric neurons that results in the secretion of pepsinogen.
2) **Histamine** from ECL (enterochromaffin - like) cells.
3) **Gastrin** that is released by G cells.
   - Somatostatin in D cells inhibits acid secretion. If Gastric pH < 3, gastric D cells release somatostatin, which inhibits acid secretion and keeps the balance by:
     1) direct effects on parietal cells and inhibiting their functions.
     2) inhibiting the release of histamine & gastrin or both.

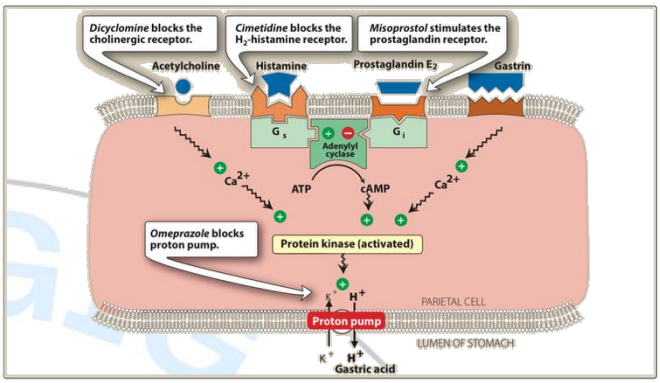


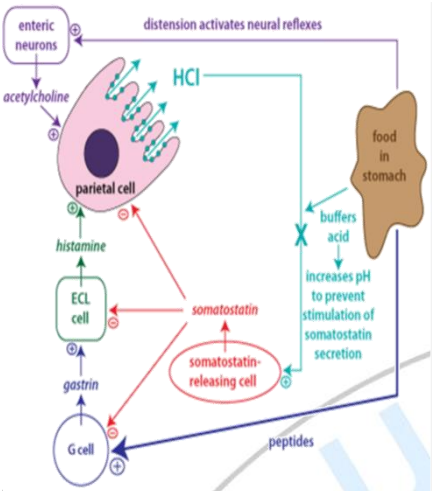
Figure 31.4
Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

➔Three phases in gastric acid secretion:

1) **Cephalic Phase:**
   - Sight, smell, taste, or thought of food **activates enteric neurons** that induce the **Ach** to be secreted and **induce parietal cells to work**.
   - In humans, the major effect of gastrin is indirect through **the release of histamine from ECL cells**, not through direct parietal cell stimulation.

2) **Gastric Phase:**
   - Food **stretches** stomach walls, activating a neural reflex to stimulate acid secretion.
   - Peptides & amino acids stimulate **G cells to release gastrin,** increasing acid secretion, and the pH will decrease.
   - Food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion, which inhibits the secretion of HCl.

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



Review: peptic ulcer disease

➔ **Peptic ulcer:** a defect in the lining of the stomach or the duodenum.

➔ Causes of Peptic Ulcer:

1) Helicobacter pylori infection (most common).
2) Drugs such as aspirin & other NSAIDs
3) Smoking, Stress, and alcohol.
4) Gastrinomas
   Gastrinomas are neuroendocrine tumors in the stomach characterized by the secretion of gastrin with **resultant excessive gastric acid production**, causing severe, recurrent peptic ulcer disease and diarrhea, a combination referred to as the **Zollinger-Ellison syndrome (ZES)**

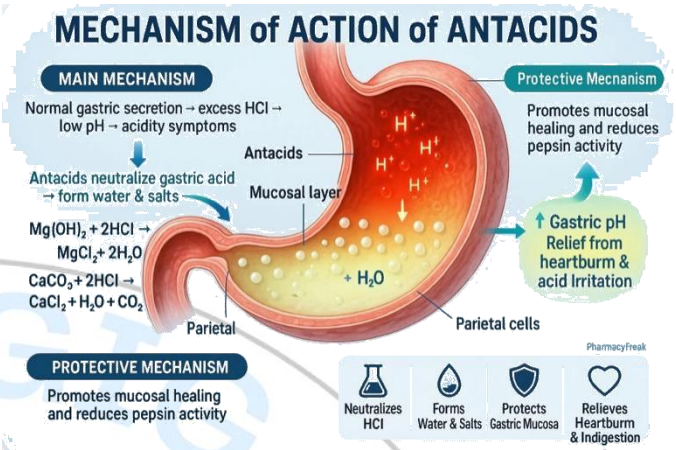
➔ Symptoms:

1) burning pain in the stomach between meals or at night, bloating, heartburn, nausea, or vomiting.
   - In severe cases, symptoms include:
2) Dark or black stool (due to bleeding)
3) Vomiting blood because of the high bleeding in the stomach.
4) Weight loss & severe pain in the mid to upper abdomen.

➔ Complications of peptic ulcer:

1) Gastrointestinal bleeding.
   Sudden large bleeding can be life-threatening.
2) Cancer (Helicobacter pylori as the etiological factor)
3) Perforation (hole in the wall)
   This case is life-threatening

Treatment options



1) **Reduce acid secretion** by agents such as H2 receptor antagonists.
2) **Neutralize** acid in the lumen with antacids.
3) **Protect the mucosa** from acid destruction.
4) **Antibiotics** to eradicate Helicobacter pylori. If this is successful, then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

Mechanism of action

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

They include:

- Aluminum-based: $AL(OH)_3 + HCL \rightarrow ALCl_3 + H_2O$ -> reacts slowly without gas formation.
- Magnesium based: $2HCL + Mg(OH)_2 \rightarrow MgCl_2 + 2H_2O$

Side effects

- **Aluminum antacids**:
  1) **constipation**
  2) **interfere with the absorption of many drugs**.
- Magnesium antacids:
  - **diarrhea**
  - **stimulates gastric release** (acid rebound)
  - Magnesium trisilicate is a slow-acting antacid, thereby **increasing the duration of action** of the drug.
- **Combination** of Magnesium & aluminum antacids is most used (No diarrhea or constipation).

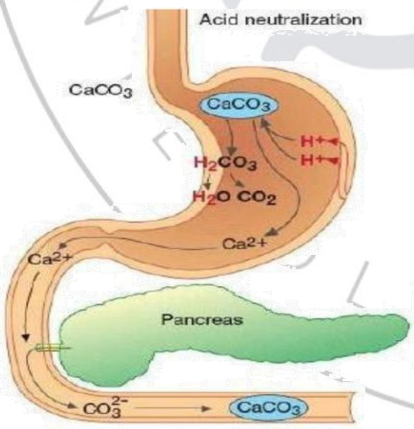
- This combination **decreases the amount of aluminum hydroxide**, thereby reducing its interference with the absorption of other drugs.
- They're contraindicated in renal insufficiency.

Magnesium Hydroxide	Aluminum Hydroxide
React slowly and without gas formation.	
Metabolic alkalosis is also uncommon.	
Magnesium salts cause diarrhea.	Aluminum salts cause constipation.
Usually given in combination, to avoid the problem of constipation caused by aluminum salts and diarrhea caused by magnesium salts.	
Contraindicated in renal failure, because these drugs are primarily excreted by the kidneys.	

- Calcium carbonate ➞ $2HCl + CaCO_3 \rightarrow CaCl_2 + CO_2 + H_2O$
  This reaction **decreases acid secretion by binding to HCL**, producing calcium chloride and carbon dioxide.

Side effects

1) Associated with "acid rebound. "
2) With excessive chronic use, it may cause **milk-alkali** syndrome with elevation of serum calcium, phosphate, urea, nitrogen, creatinine & bicarbonate levels, so it should be given with caution, ensuring adherence to the prescribed dose.



- Sodium bicarbonate-based ➞ $NaHCO_3 + HCL \rightarrow NaCl + H_2O + CO$
- It **should be avoided in patients with hypertension** as it counteracts diuretic therapy.

- Short duration of action, followed by acid rebound.

Side effects

1) Highly absorbed, potentially causing **metabolic alkalosis**.
2) CO2 results in **belching**.

H2 receptor antagonist

In normal situations, acetylcholine and gastrin induce the release of Histamine, which binds to H_2 receptors and **activates the proton pump** (K+/H+) to produce HCl.

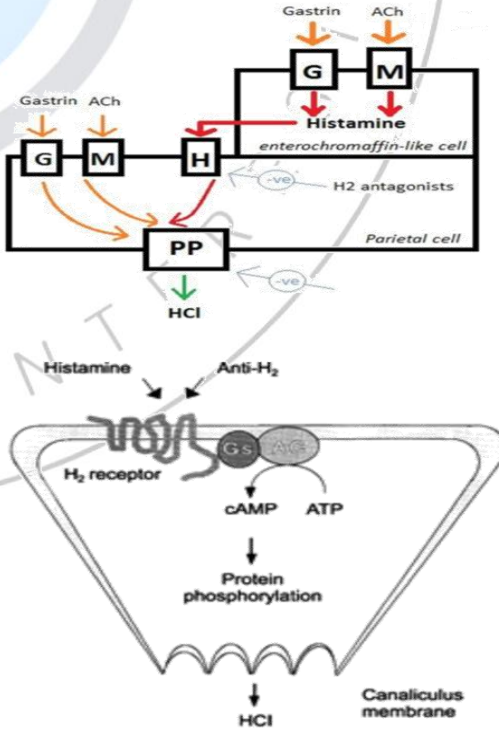
Mechanism of action

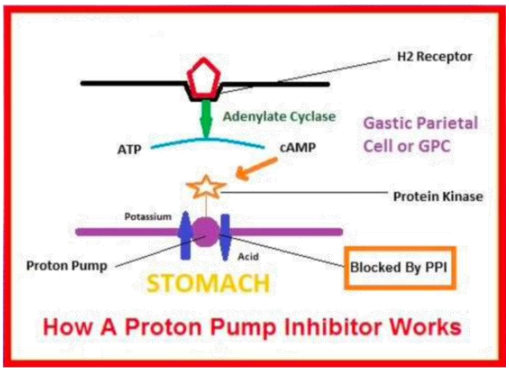
When H2 receptor antagonists are used, **they block the action of histamine**, thereby preventing activation of the proton pump and reducing HCL production.

They particularly interrupt the downstream signaling pathway, particularly the protein Phosphorylation, which stops HCL production.

Selective competitive inhibitors of the parietal cell H_2 receptor:

1) suppress basal and meal-stimulated acid secretion in a dose-dependent manner.
2) decrease the volume of secretion and pepsin concentration.





➔ **H_2 receptor antagonists include:**

1) Cimetidine
   - Prototype drug – associated with many problems.
2) Ranitidine.
3) Famotidine.
   - 50% first-pass metabolism bioavailability.
4) Nizatidine
   - has little first-pass metabolism.

Duration of action: **~12 hours**

They inhibit 60-70% of the total 24-h acid secretion.

- **90% of nocturnal acid.** *Nocturnal acid is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes.*
- **60% of daytime, meal-stimulated, acid**

Comparison between H2 receptor antagonists and proton pump inhibitors:

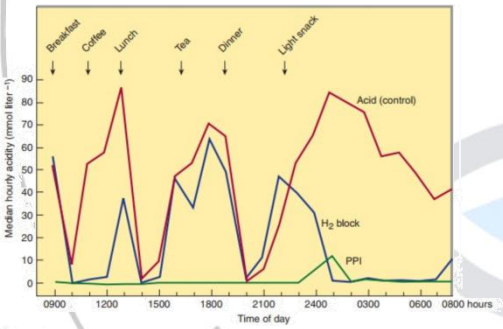


FIGURE 62–2 Twenty-four-hour median intragastric acidity pretreatment (red) and after 1 month of treatment with either ranitidine, 150 mg twice daily (blue, H_2 block), or omeprazole, 20 mg once daily (green, PPI). Note that H_2-receptor antagonists have a marked effect on nocturnal acid secretion but only a modest effect on meal-stimulated secretion. Proton pump inhibitors (PPIs) markedly suppress meal-stimulated and nocturnal acid secretion. (Redrawn from data in Lanzon-Miller S et al: Twenty-four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment Pharmacol Ther 1987;1:239.)

With **H2 receptor antagonists**, acid secretion **<u>fluctuates</u>** throughout the day due to the intake of different meals several times.

With **proton pump inhibitors**, there is a **<u>stable level of acidity</u>**. This is why we <u>prefer</u> proton pump inhibitors over the H2 receptor antagonists.

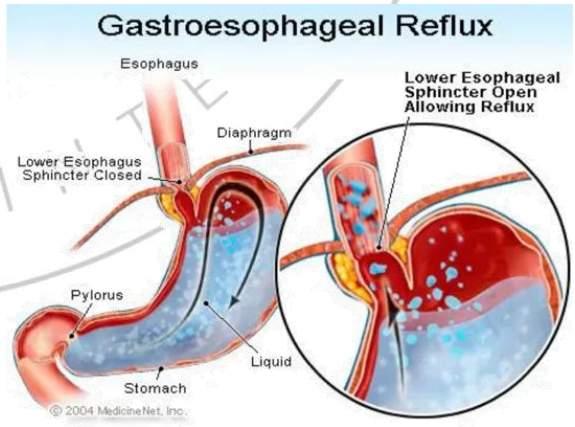
H_2 receptor antagonists block the receptor, which blocks the downstream pathway of acid secretion.

Proton pump inhibitors bind to the H+/K+-ATPase enzyme system (proton pump) of the parietal cell and **suppress the secretion of hydrogen ions into the gastric lumen**, thereby reducing the acidity of the stomach.

Clinical Uses

1) **Gastroesophageal Reflux:**
   - *Prophylactically*, **before meals**.
   - Achieves healing for erosive esophagitis, which is the inflammation of the esophagus because of the acid reflux, in less than 50% of patients.
   - Proton pump inhibitors are <u>preferred</u>.

<u>GERD</u>: Normally, the LES is closed which prevents acid reflux into the esophagus; in pathologies that make it loose, allowing acid reflux can lead to GERD



GERD is a condition in which the liquid content of the stomach regurgitates into the esophagus, often causing heartburn.

2) **Non-Ulcer Dyspepsia.**

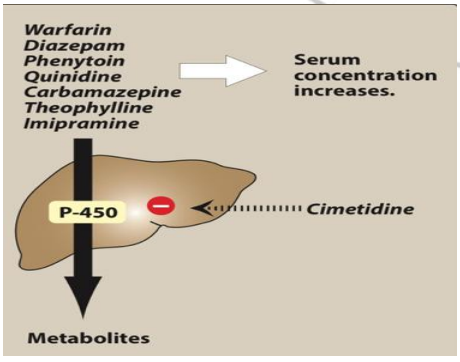
3) **Stress - Related Gastritis**:
   - Can prevent bleeding, usually given IV.
4) **Peptic Ulcer Disease**:
   - Replaced by PPI.
   - H2 receptor antagonists are no longer used. Its healing rate is greater than 80-90% after 6-8 weeks, which is considered a long time.
   - Not effective:
     - In the presence of H. pylori infection.
     - If NSAIDs are continued, and they're the cause of the peptic ulcer.

Adverse Effects

1) Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia, and constipation.
2) CNS: Confusion, hallucinations occur only with IV **cimetidine** in elderly patients in the ICU.
3) Endocrine Effects: only **cimetidine** because it **inhibits estradiol metabolism**, and can **increase prolactin serum** levels, which can be associated with infertility cases among women.
4) In pregnant and nursing mothers, they can cross the placental barrier and appear in breast milk.
5) Rarely can cause bradycardia and hypotension.

Drug Interactions

1) **Cimetidine** can inhibit cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6, and CYP3A4), which can **increase half life of many drugs**.
   - **Ranitidine** binds 4-10 times less.
   - **Nizatidine and famotidine** binding is negligible



Proton pump inhibitor, PPI

Very efficacious and safe drugs.
They include:
1) Omeprazole (oral).
2) Rabeprazole (oral).
3) Lansoprazole (oral and IV).
4) Pantoprazole (oral and IV).
5) Esomeprazole (oral and IV).

They are formulated mainly as a **prodrug** that is released in the intestine.
Some formulas of PPI drugs are in the form of **Immediate-Release Suspension,** which results in rapid response (rapid onset of action). However, they are less common in comparison with the prodrug formula.

Pharmacokinetics and Mechanism of Action
They are **lipophilic** weak **bases** (pKa 4-5).

- **Absorption and activation**

In the intestines, they get absorbed and then 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 is responsible for the drug's effect on the proton pumps, covalently binds the H+/K+ ATPase enzyme, and **inactivates it**, thereby **preventing the pumping of protons and increasing the acidity**.

- **Notes**

1) Rabeprazole has immediate release, while omeprazole has faster onsets of action.
2) These drugs should be given one hour before breakfast.
3) Have **short half-lives**, but **the effect lasts for 24 hours** (given once daily) due to irreversible inhibition.

Pharmacodynamics
- Inhibit **both fasting and meal-stimulated secretion** because they **block the final common pathway** of acid secretion (90-98% of 24-hour secretion).
- This dual inhibition guarantees a more efficient effect of PPIs

➔ **Clinical Uses:**

1) **Gastroesophageal Reflux (GERD)**
They are **the most effective** agents in all forms of GERD and complications.

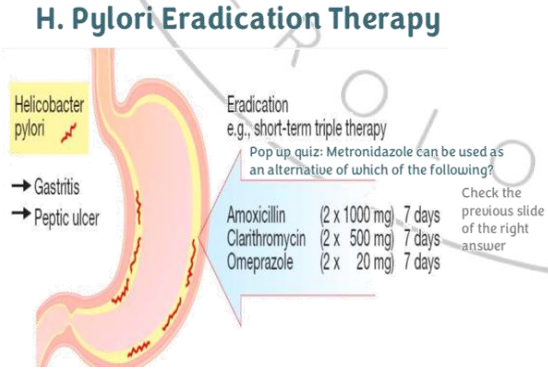
2) **Nonulcer Dyspepsia**
Modest activity.
10-20% more beneficial than a placebo.

3) **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.
In all cases of stress-related ulcers, the **PPIs are considered an effective treatment**

4) **Gastrinoma and Other Hypersecretory Conditions**
Usually, **high doses of omeprazole** are used.

5) **Peptic Ulcer Disease:**
They heal more than 90% of cases within 4-6 weeks.
In H. pylori - associated ulcers, they:
    1) **Reduce acidity**
    2) **Eradicate H. pylori** by direct antimicrobial activity and by lowering the MIC (Minimum Inhibitory Concentration) of the antibiotics.

Triple Therapy: PPI twice daily, Clarithromycin 500mg twice daily, Amoxicillin 1gm twice daily, OR Metronidazole 500mg twice daily.



In NSAID-associated ulcers, PPIs promote ulcer healing despite continued NSAID use. Also used to **prevent ulcer complications** of NSAIDs.

In Rebleeding peptic ulcer:
They are used as Oral or IV therapy.
High pH caused by PPIs may enhance coagulation and platelet aggregation, therefore stopping the bleeding process.

Adverse Effects

1) Diarrhea, headache (normal adverse effects associated with PPIs), abdominal pain, not teratogenic in animals, but not used in pregnancy.

2) Reduction of cyanocobalamin (vitamin B12) absorption because acid is needed for its absorption in a complex with intrinsic factor. This results in an **increased risk of GI and pulmonary infection**, as vitamin B12 can help balance immune responses to better fight viral and bacterial infections. The solution is to take vitamin B12 supplements from time to time while using PPIs.

3) Elevated gastric pH may also impair the absorption of calcium carbonate. 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

4) Increased serum gastrin levels, which were associated with:
    a. Hyperplasia of ECL cells.
    b. Carcinoid tumors in rats, but no such findings were recorded in humans.
    c. Increase the proliferative rate of colonic mucosa.
    d. Chronic inflammation in the gastric body.
    e. Atrophic gastritis and intestinal metaplasia.

This happens because PPIs block acid secretion by inhibiting the H^+/K^+ ATPase pump in parietal cells of the stomach. Reduced gastric acid → less negative feedback on G-cells, **G-cells respond by secreting more gastrin to try to stimulate acid production**. This leads to **hypergastrinemia** (elevated gastrin levels).

Drug Interactions

1) May affect the absorption of drugs due to **decreased gastric acidity**, such as digoxin and ketoconazole.
2) **Omeprazole** can inhibit the metabolism of drugs such as diazepam and phenytoin.

Rabeprazole and pantoprazole have no significant interactions. Therefore, rabeprazole and pantoprazole are **the PPIs of choice if the patient needs to take other drugs as well**.

Nausea

Diarrhea

Headache

GI disturbance

Bone Fractures
(increased risk
with long-term use:
hip, wrist, and spine)

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Pharmacology

Laxatives, Antidiarrheal Agents & IBS management

Written by: Mohammad Talal Harahsheh

Edited by: Rawan Fratekh

[Overview]

➔ **Outline of Laxatives**

1) Non-pharmacological management of constipation

2) Definition of laxatives and their classification

1. **Bulk-forming agents**
2. **Stool surfactant agents**
3. **Osmotic laxatives**
4. **Stimulant laxatives**
5. **Serotonin-related pro-kinetic laxatives**

[Non - Pharmacologic Management of Constipation]

These measures are recommended before initiating pharmacologic therapy

1) High-fiber diet
Fiber increases stool bulk and stimulates bowel motility

2) Adequate fluid intake
Water softens stool and prevents fecal hardening

3) Regular exercise
Physical activity promotes intestinal motility

4) Responding to the urge to defecate
Ignoring the defecation reflex may worsen constipation

Laxatives and their classification

Laxatives are agents used to **facilitate bowel movement and relieve constipation** by increasing stool bulk, softening stool, increasing intestinal fluid, or stimulating intestinal motility

Classification of Laxatives

Laxatives are divided into the following major classes:

1. Bulk-forming laxatives
2. Stool surfactant agents (stool softeners)
3. Osmotic laxatives (purgatives)
4. Stimulant laxatives (cathartics)
5. Serotonin-related pro-kinetic laxatives

Bulk-Forming Laxatives

Bulk-forming laxatives are indigestible hydrophilic colloids that absorb water and form a bulky gel in the intestinal lumen.

Mechanism of Action

- **Absorb water** in the intestine
- Form a **bulky, emollient gel**
- Distend the colon and stimulate peristalsis and bowel movement.

Peristalsis refers to coordinated intestinal contractions that move intestinal contents forward.

Adverse Effects

1) Bloating
2) Flatus

Examples

Natural plant products:
1) Psyllium
2) Sterculia (Normacol)
3) Methylcellulose

Synthetic fiber:
1) Polycarbophil

Stool Surfactant Agents (Stool Softeners)

These agents facilitate the mixing of water and lipids with stool, making fecal material softer and easier to pass.

Mechanism of Action

- **Allow water and lipids to penetrate stool**
- Reduce stool hardness
- Facilitate defecation

Administration
1) Oral
2) Rectal

Examples
1) Docusate
2) Glycerin suppository
3) Mineral Oil

Mineral oil is a clear viscous oil that lubricates fecal material.

Mechanism

- **Coats stool surface**
- Retards water absorption from stool
- Maintains stool softness

Clinical Use
- Prevention and treatment of fecal impaction.

Fecal impaction refers to severe constipation with a large, hardened stool mass obstructing the rectum.

Adverse Effects

1) **Aspiration** → lipoid pneumonia.
Occurs if oil enters the lungs during swallowing.

2) **Impaired absorption of fat-soluble vitamins** (A, D, E, K).

Osmotic Laxatives (Purgatives)

Osmotic laxatives are non-absorbable substances that draw water into the intestinal lumen.

Mechanism of Action

- **Increase osmotic pressure in the intestine**.
- Increase fecal water content.
- Soften stool and promote bowel movement.

Magnesium Salts
Magnesium oxide (Milk of Magnesia.)
Large doses of Magnesium citrate or Sodium phosphate may cause **purgation**.
Purgation is rapid bowel evacuation within 1–3 hours.

Adverse Effects

1) Hypermagnesemia → Elevated magnesium levels in blood.
2) Purgation may lead to volume depletion.

Osmotic Sugars

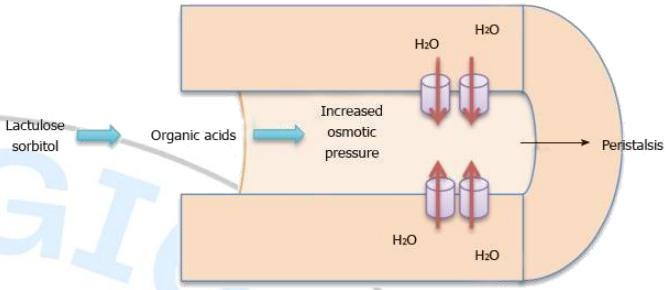
These include:
1) Sorbitol
2) Lactulose

Mechanism

- Metabolized by intestinal bacteria
- Produce osmotic effect → **increase stool water**.

Adverse Effects

1) Severe flatus
2) Abdominal cramps
These occur due to bacterial fermentation in the colon.



Balanced Polyethylene Glycol (PEG)

PEG is an inert, non-absorbable osmotic compound which can include electrolytes like sodium sulfate, chloride, bicarbonate and sodium chloride.

Characteristics

1) Does not cause electrolyte imbalance
2) Does not cause intravascular fluid shifts
3) Minimal cramps or gas

Uses
Complete colonic cleansing before endoscopy.

Administration
For bowel preparation
- Rapid ingestion of 4 liters over 2–4 hours

For chronic constipation:
- PEG powder mixed with water or juice

Stimulant Laxatives (Cathartics)

Stimulant laxatives directly stimulate the enteric nervous system.

Mechanism of Action

- **Increase intestinal motility**
- Stimulate colonic fluid and electrolyte secretion

Long -Term Risks

Chronic use may lead to:
1) Dependence on laxatives
2) Damage to myenteric plexus

Myenteric plexus is the neural network controlling intestinal motility.
This may result in:
1) Colonic atony
2) Colon dilation

Clinical Uses

1) Neurologically impaired patients
2) Bed-bound patients in long-term care facilities

Anthraquinone Derivatives

These include:
1) Aloe
2) Senna
3) Cascara

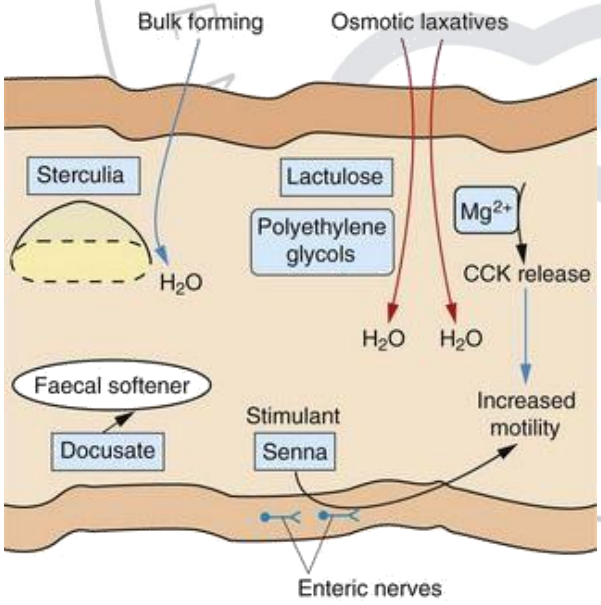
Characteristics

- Poorly absorbed
- Hydrolyzed in intestine
- Produce bowel movement in 6–12 hours

Adverse Effect

- Melanosis coli → which is **brown pigmentation** of the colon due to chronic stimulant laxative use.

Important note
They are **NOT carcinogenic**



Castor Oil

Castor oil is hydrolyzed in the upper intestine to produce **ricinoleic acid**.

Mechanism

- Ricinoleic acid acts as **a local intestinal irritant**
- Stimulates intestinal motility and evacuation

Clinical Use

- Previously used for bowel cleansing before procedures.

Serotonin-Related Prokinetic Agent
Brief review of normal physiology
Food distends the gut leading to stimulation of **5-HT (serotonin)** release from EC cells.

Serotonin (5-HT) can stimulate multiple receptors in the GI tract causing multiple effects:

1) **Stimulation of 5-HT3 receptors** activates the **extrinsic** afferent nerves causing **nausea, vomiting or abdominal pain**.

2) **Stimulation of 5HT1P receptors** of the **intrinsic** primary afferent nerves (IPANs) which activates the enteric neurons responsible for **peristaltic and secretory reflex activities**.

3) **Stimulation of 5-HT4 receptors** on **presynaptic** terminals of IPANs leads to the release of ACh and calcitonin gene-related peptide **promoting gastrointestinal motility**.

Tegaserod

Tegaserod is a serotonin 5-HT4 partial **agonist**.

Mechanism of Action

- Acts on **presynaptic 5-HT4 receptors** in intrinsic primary afferent neurons which enhances the release of their neurotransmitters.
Effects include:
1) Increased release of neurotransmitters
2) Proximal bowel contraction (via ACh and Substance P)
3) Distal bowel relaxation (via nitric oxide and VIP)

These effects enhance intestinal motility.

Additional Effects

1) Promotes gastric emptying
2) Accelerates small and large bowel transit
3) Stimulates cAMP-dependent chloride secretion → increases stool liquidity

Clinical Uses

1) Chronic constipation
2) Non-ulcer dyspepsia
3) Gastroparesis
4) Irritable bowel syndrome

Adverse Effects

- Diarrhea in ~9% of patients which usually resolves within a few days

Limitation

- High cost

[Overview]

➔ **Outline of Antidiarrheal agents**
- **1) General considerations**
- **2) Antidiarrheal agents**
  1. **Opioid agonists**
  2. **Kaolin and Pectin**
  3. **Bile salt-binding resins**
  4. **Octreotide**

[General consideration]

Antidiarrheal agents are medications that are used to **treat mild to moderate acute diarrhea**.
They can also be used to **control chronic diarrhea** in patients with irritable bowel syndrome or inflammatory bowel disease.

These medications **should NOT** be used in the presence of infectious diarrhea.

[Antidiarrheal agents]

Most commonly include
1) Opioid agonists
2) Kaolin and Pectin
3) Bile salt-binding resins
4) Octreotide
5) Loperamide

Opioid agonists

Opioids exert significant constipating effects via inhibiting the presynaptic cholinergic nerves peripherally.

This leads to constipation / counteracting diarrhea by:
1) **Increasing colonic transit time** (*the time it takes stool to pass through the colon*).
2) **Increased fecal water absorption**.
3) **Decreased mass colonic movement and gastrocolic reflex**.

Important note
Opioids act on the central nervous system and have potential **addictive effects**.
We usually combine them with atropine to reduce dependence.

Loperamide
An common opioid agonist antidiarrheal that does **NOT** cross the blood-brain barrier. It does not have analgesic or addictive effects.

Diphenixylate
An opioid agonist antidiarrheal.
It has CNS effects and **can cause dependence**.

Kaolin and Pectin

Kaolin is a natural hydrated magnesium silicate, **Pectin** is an indigestible carbohydrate derived from apples.

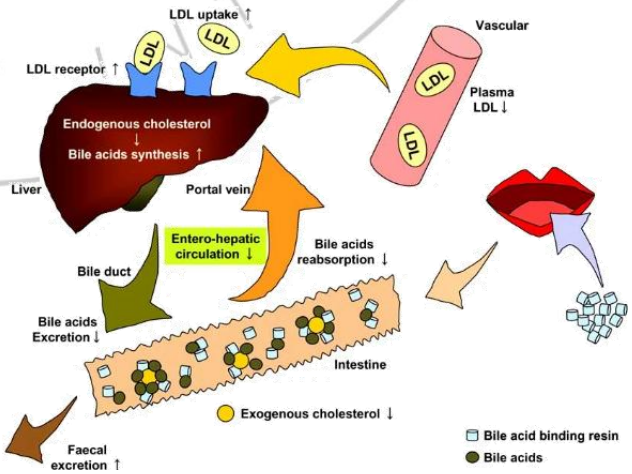
Mechanism of action

They both absorb bacteria, toxins, and liquids.

Administration

- Usually taken combined - Kaopectate.
- Taken far from other medications due to potential effects on their action.

Bile salts-binding resins



Bile acid resins are used to treat diarrhea caused by malabsoprtion of bile salts.

They include:

1) Choestyramine
2) Colisipol

Mechanism of action

These drugs **bind bile salts and prevent them from causing water secretion** which leads to the diarrhea.

Side effects

1) Bloating
2) Flatulence
3) Constipation and fecal impaction
4) Drug and fat malabsoprtion

Octreotide

Octreotide is a synthetic peptide with actions similar to somatostatin (a somatostatin analogue).

Somatostatin is a 14-amino acid peptide released from the GI tract and pancreas, as well as the hypothalamus.

Its functions include:

1) Inhibits the release of many hormones
2) Reduces intestinal fluids and pancreatic secretions
3) Slows GI tract and gallbladder contractions
4) Contracts blood vessels
5) Inhibits secretion of some anterior pituitary hormones

Clinical use

1. **Inhibition of endocrine tumor effects**

Carcinoid tumors cause secretory diarrhea and systemic symptoms like flushing and wheezing.

2. **Treatment of diarrhea due to vagotomy or dumping syndrome and AIDs**.

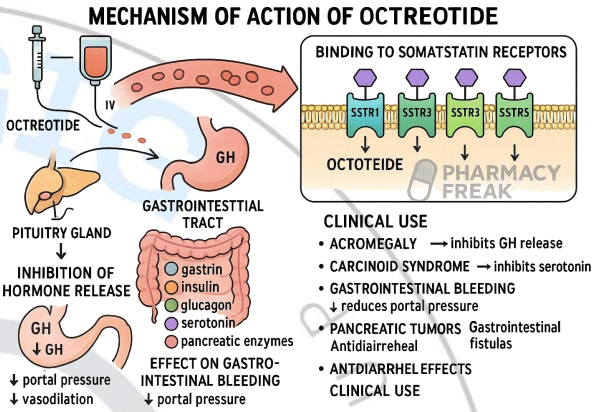
Vagotomy means cutting the branch of the vagus nerve that controls gastric acid secretion

Dumping syndrome is a condition in which food, especially that high in sugar, moves from the stomach to the small intestines rapidly.

3. **Stimulates motility** in small bowel bacterial overgrowth or intestinal pseudo-obstruction due to scleroderma.

Scleroderma is an autoimmune condition the results in hard, thickened areas of the skin and fibrosis in the parts of the GI tract.

4. **Used in the management of pituitary tumors and GI bleeding**.



[Overview]

➔ **Outline of Irritable Bowel Syndrome management.**

1) Introduction to Irritable Bowel Syndrome (IBS)
2) Pharmacologic therapies for IBS

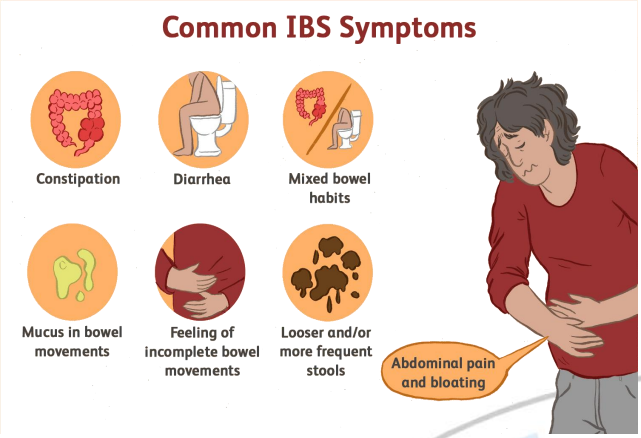
[Introduction to Irritable Bowel Syndrome (IBS)]

IBS is an idiopathic, chronic disorder characterized by:

1) Abdominal discomfort/cramps
2) Bloating
3) Abdominal distention
4) Change in bowel habits (constipation/diarrhea)

It can be either:

1) **Diarrhea-dominant** where patients mainly complain of diarrhea.
2) **Constipation-dominant** where patients mainly complain of constipation
3) **Mixed**.



[Pharmacologic therapies for IBS]

IBS is a chronic condition that has no definitive cure. Medications are usually **used to manage the symptoms** and are tailored for patients needs.

Antispasmodic or Anticholinergic medications

These include:
1) Dicyclomine
2) Hyoscyamine

Mechanism of action

- **They inhibit muscarinic cholinergic receptors** in the enteric plexus and on smooth muscle cells, relieving abdominal discomfort.

They are usually used at low doses and exhibit minimal side effects.

Serotonin 5-HT_3-Receptor antagonists

These include:
1) Alosterone

Mechanism of action

- They **block the 5-$HT3_3$ receptor** present in the **afferent pain fibers in the extrinsic sensory neurons** and **the terminals of enteric cholinergic neurons**.
- The receptor is also present in the CNS and is **involved in the central response to visceral afferent stimulation**.

Clinical use

- It's used in **women** with severe, **diarrhea-predominant** IBS. Efficacy is unknown in men.
- It has a **long duration of action**.

Adverse effects

1) Ischemic colitis
It is a condition that occurs when **blood flow to the parts of the large intestines is temporarily reduced**, leading to ischemia.

2) **Severe constipation** that might require hospitalization and surgery.

Serotonin 5-HT_3 receptor agonists

These include:
1) Tegaserod(mentioned previously)

Clinical use

- Used for short-term treatment of **constipation-predominant IBS** in **women**.
- It reduces pain, bloating and hardness of stool.
- It is expensive.

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Pharmacology

Antiemetic Agents

Written by: Mohammad Talal Harahsheh

Edited by: Rawan Fratekh

[Overview]

➔ **Outline of Laxatives**

1) Definition of antiemetic agents and physiology of vomiting

2) Classes of antiemetics

1. **Serotonin 5-HT-$_3$ receptor antagonists**
2. **Neurokinin-1 (NK1) Receptor Antagonists**
3. **Cannabinoids**
4. **Antipsychotic Drugs**
5. **Benzodiazepines**

[Definitions of Antiemetic Agents and physiology of vomiting]

Antiemetics are drugs used to **prevent or treat nausea and vomiting** caused by various medical conditions or treatments

Nausea and vomiting may occur in many situations, including:

1) Adverse drug reactions
2) Systemic infections or disorders
3) Pregnancy
4) Vestibular dysfunction
5) Central nervous system disorders or increased intracranial pressure
6) Peritonitis
7) Hepatobiliary disease
8) Radiation therapy or chemotherapy
9) Gastrointestinal obstruction, infections, or motility disorders

Pathophysiology of Vomiting

Vomiting is **coordinated by the vomiting center in the brainstem**.

This center interacts with:
- **Cranial nerve VIII** (vestibular system).
- **Cranial nerve X** (vagus nerve).
- Neural networks in the n**ucleus tractus solitarius**.

These networks control:

1) Respiratory centers
2) Salivatory centers
3) Vasomotor responses associated with vomiting

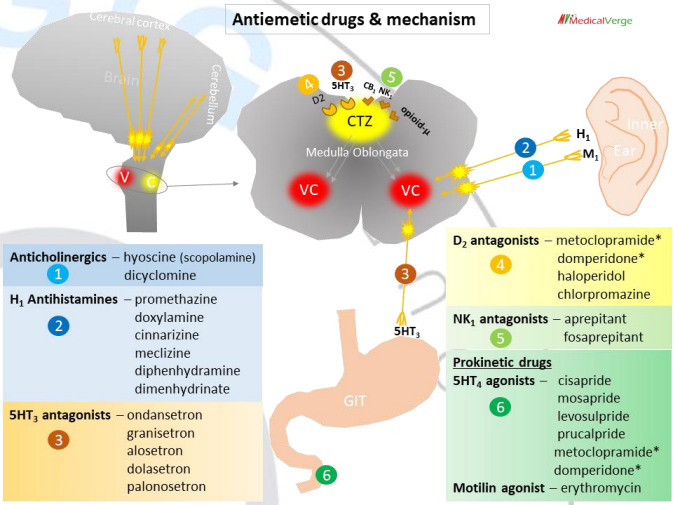
Important Receptors in the Vomiting Center

The vomiting center contains high concentrations of:

1) M1 (**muscarinic**) receptors
2) H1 (**histamine**) receptors
3) NK1 (**neurokinin-1**) receptors
4) 5-HT3 (**serotonin**) receptors

These receptors are the targets of most antiemetic drugs.

[Classes of antiemetics]



Serotonin 5-HT3 Receptor Antagonists

These include:

1) Ondansetron
2) Granisetron

Mechanism of Action

These drugs work by

1) **Blocking central** 5-HT3 receptors
2) **Blocking peripheral** 5-HT3 receptors in the GI tract

This action **prevents vagal stimulation of the vomiting reflex**, particularly during chemotherapy

Clinical Uses

1) Prevention of **chemotherapy-induced** nausea and vomiting
2) Prevention of **postoperative** nausea and vomiting

Their effectiveness is **enhanced** when combined with:

1) Dexamethasone
2) NK1 receptor antagonists

Limitations

- Less effective in motion sickness and other non-vagal causes of vomiting.

Adverse Effects

Common adverse effects include:

1) Headache
2) Dizziness
3) Constipation

Neurokinin-1 (NK1) Receptor Antagonists

These include:
- Aprepitant

Mechanism of Action

- Blocks NK1 receptors in the area postrema of the brainstem.
The **area postrema** is a chemoreceptor trigger zone involved in the vomiting reflex.
This **inhibits the vomiting reflex triggered by chemotherapy**.

Clinical Use

- Prevention of **acute and delayed chemotherapy-induced nausea and vomiting**.

Usually used in combination with:

1) 5-HT3 receptor antagonists
2) Corticosteroids

Cannabinoids

These include:

1) Dronabinol
2) Nabilone

Mechanism of action

- The exact antiemetic mechanism is not completely understood.
- They **act centrally and affect the brain pathways regulating nausea and vomiting**.

Clinical Use

- Treatment of **chemotherapy-induced vomiting when other drugs are ineffective**.

Adverse Effects

Because these drugs are **psychoactive**, they may cause:

1) Euphoria
2) Dysphoria
3) Sedation
4) Hallucinations
5) Dry mouth
6) Increased appetite

Antipsychotic Drugs

These include:

1) Prochlorperazine
2) Promethazine
3) Droperidol

Mechanism of Action

These drugs exert antiemetic effects by:

1) Blocking dopamine receptors
2) Blocking muscarinic receptors

They also have **antihistamine activity**, which contributes to their **sedative** effect

Benzodiazepines

These include:

1) Lorazepam
2) Diazepam

Mechanism of action

- These drugs **reduce vomiting related to anxiety**.
- They act by **producing sedation and anxiolysis**, which helps control nausea associated with stress or anticipation of chemotherapy.

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Pharmacology

Anti-viral medications

Written by: Noura Mohammad Alqaisi

Edited by: xx

[Overview]

➔ **Outline anti-viral medications:**

1) **Overview of viruses and the most encountered GI viral infections**

[Overview of viruses and the most encountered GI viral infections]

Viruses are obligate intracellular microbes that use the host cell's biochemical processes to sustain their viability.
A **virion** is a mature virus that can exist outside a host cell and maintain its infective properties.

Viruses can be classified based on their genetic composition, morphology, multiplication site, and many others.

1) **DNA viruses**: adenovirus (cold and conjunctivitis), hepadnaviruses (Hepatitis B), herpesviruses (CMV, chickenpox), papillomaviruses (warts).
2) **RNA viruses**: arbovirus (yellow fever), arenavirus (meningitis), orthomyxoviruses (influenza), paramyxoviruses (measles, mumps), picornaviruses (meningitis, cold), rubella virus (German measles), retrovirus (AIDs).

Cytomegalovirus (CMV)

- **Clinical manifestation**: It mostly causes a GI infection in both immunocompetent and immunocompromised individuals.
  1) Immunocompetent ➞ mostly asymptomatic
  2) Immunocompromised/neonates/elderly ➞ can cause severe systemic disease
- **Latency**: in macrophages after the primary infection➞ can reactivate later.

Herpes simplex virus (HSV)

- **Clinical manifestation:** It mostly causes an infection in the esophagus and anorectal region in both immunocompetent and immunocompromised individuals.

HSV esophagitis often presents with an **acute onset of nausea and vomiting**, **chest pain**, and, less commonly, **GI bleeding**, even **esophageal perforation**.

1) Immunocompetent ➞ mostly asymptomatic
2) Immunocompromised ➞ can cause disseminated disease and are at risk for severe complications

Adenovirus

- Enteric Adenovirus **types 40 and 41** are transmitted through the **feco-oral route**.
- **Epidemiology**: primarily affects infants and young children.
  In immunocompromised → high mortality rate
- **Clinical manifestations**: **watery diarrhea** for 5 –12 days
  In pediatric patients ➞ can cause **intestinal obstruction** due to lymphoid hyperplasia.

Rotaviruses (fatal if not treated)

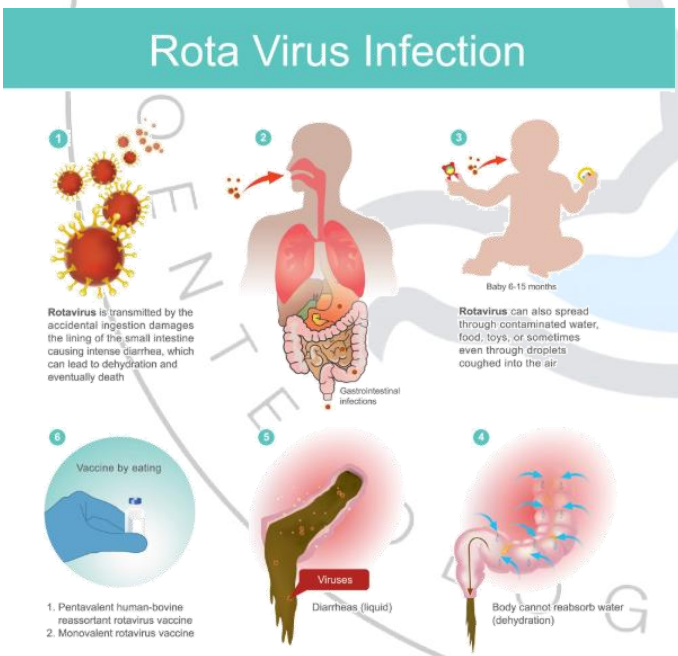
- It is a double-stranded RNA virus from the family of Reoviridae.
- **Epidemiology:** mostly affects children,
  The elderly are vulnerable due to weakening immune system → infections can spread rapidly in nursing homes.
  High-risk patients: malnourished children are more susceptible to future diarrheal illness → higher risk of death.
  Adults who were previously infected with the virus do not develop a second infection due to **immune memory**.

- **Incubation/duration:** ~2 days incubation, lasts 3–8 days (~1 week)
- **Transmission:** from family members with subclinical or clinical disease, or contaminated surfaces (virus survives for some time)

- **Clinical manifestations: mainly fever, vomiting, diarrhea**.
  The virus survives in the stomach but primarily in the **small intestine** villi; it can cause **food intolerance**, especially lactose
- **Complications: severe fluid loss**, dehydration, **death** if untreated; repeated infections ➞ **malnutrition** in children, especially in developing countries
- **Prevention:** national vaccination programs reduce disease in children and daycare outbreaks.

- 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.

- **Diagnosis**: most cases are self-limited and do not require further evaluation. Additional testing is only needed for confirmation, suspected outbreaks, or severe illness.
  1) **Enzyme immunoassay**, which detects the virus from fecal samples (the most common)
  2) Latex agglutination assays
  3) Electron microscopy
  4) RT- PCR (Reverse Transcription Polymerase Chain Reaction)
- **Treatment** (the general principle applies to all GI viral infections):
  1) **Rehydration** is key: oral rehydration therapy is a solution that contains water and electrolytes to replenish GI losses and is usually used in children.
  2) **Preventive** vaccination is also available for rotavirus, 2 doses.
     The first dose: **between six and 15 weeks of age**
     The second: **before 32 weeks**



Norovirus (highly contagious; cruise ship outbreaks)

- Family: **calicivirus**, commonly known as Norwalk virus. It is a **highly contagious virus** that often spreads in confined spaces (cruise ships, nursing homes).
- **Epidemiology**: infants, young children, elderly
- **Transmission: fecal-oral**, **direct contact**, contaminated surfaces, contaminated food.
- **Resistant:** not killed by standard disinfectants ➞ risk remains high after cleaning
- **Incubation/duration: 12–48 hours after** exposure; illness is usually **mild**, clears within a couple of days
- **Clinical manifestations: watery diarrhea, mild cramps, fever**, sometimes **projectile vomiting**
- **Complications:** dehydration may occur, especially in vulnerable patients

- **Diagnosis:** RT-qPCR preferred; EIA can be used for rapid testing, but PCR confirmation is needed.
- **Treatment:** no medications; supportive care with **rehydration** and **electrolyte replacement**.
- **Prevention:** good hygiene, hand washing, and careful food preparation.

Additional information regarding anti-viral medications is not covered in the lecture.

Ganciclovir (Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability)
Clinical use: CMV, especially in patients who are immunocompromised.
Adverse events: Myelosuppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir.
Mechanism of resistance: Mutated UL97 viral kinase.

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Pharmacology

Antiprotozoal medications

Written by: Mohammad Talal Harahsheh

Edited by: Rawan Fratekh

[Overview]

➔ **Outline of antiprotozoal drugs**
- **1) Selected protozoal diseases**
- **2) Classes of oral antiprotozoal drugs**
  1. **Antiprotozoal drugs**
  2. **Antimalarial drugs**

Selected protozoal diseases

Protozoa are single-celled parasitic organisms that can infect the gastrointestinal tract and other organs.

Protozoal infections are a major cause of disease worldwide, especially in areas with poor sanitation.

These infections may also be seen in **migrant workers** or **individuals returning from endemic regions**.

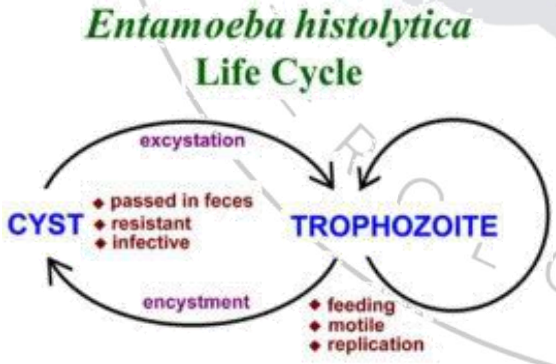
Amebiasis

Amebiasis is an infection caused by **Entamoeba histolytica**.

The parasite exists in two forms:

1) Cyst form
Infective form transmitted through contaminated food or water.

2) Trophozoite form
Motile **invasive** form that damages intestinal tissue.



Pathogenesis

After ingestion of cysts:
1) The cyst releases trophozoites in the intestine.
2) Trophozoites **invade** the intestinal mucosa.
3) They cause tissue destruction and inflammation.

The infection may range from **asymptomatic colonization to severe dysentery**, with frequent passage of bloodstained stool.

Clinical Manifestations

Possible presentations include:
1) **Asymptomatic** intestinal infection
2) Mild to moderate **colitis**
3) Severe amebic **dysentery**
   Frequent passage of **blood-stained stool**.
4) **Ameboma**
   Tumor-like **inflammatory mass** in the intestine
5) **Extraintestinal spread**
   Trophozoites may spread to the liver via the portal vein and cause **acute amebic hepatitis** or for **amebic liver abscess**.

Patients may continue to **excrete cysts for years after resolution of their acute infection**, which makes them a hazard to themselves and other.

Treatment of Amebiasis
Management depends on the type of infection

1) **Asymptomatic** Intestinal Infection
Treatment requires a luminal **amebicide** to eradicate cysts.
Examples:
1) Diloxanide furoate
2) Iodoquinol
3) Paromomycin

2) **Amebic Colitis**
Treatment of choice:
1) Metronidazole
2) In addition to a luminal amebicide.
This combination **eliminates both tissue trophozoites and luminal cysts**.

Alternative drugs:
1) Tetracyclines
2) Erythromycin
These are used in **moderate** cases but are not effective against extraintestinal disease.

Dehydroemetine or timeline are other medications that used to be used but are now avoided due to their **toxicity**.

Balantidium coli

A trophozoite that causes **superficial necrosis and/or deep ulceration in the mucosa** and submucosa of the **large intestines**.

Clinical presentation

- In **healthy, immunocompeten**t individuals → nausea, vomiting, abdominal pain, and diarrhea.

- In **immunosuppressed or nutritionally-stressed** patients → severe dysentery.

[Classes of oral antiprotozoal drugs]

Oral antiprotozoal medications are generally classified into:

1) Miscellaneous antiprotozoals
2) Antimalarial drugs

Some medications, such as metronidazole and tetracycline, can double as treatment for certain bacterial infections.

Antiprotozoals

The commonly used miscellaneous antiprotozoal drugs include:

1) Metronidazol
2) Tinidazole
3) Nifuratel

Metronidazole

Metronidazole is **the drug of choice** for tissue infections caused by Entamoeba histolytica.

Metronidazole can be used to treat:

1) Intestinal amebiasis
2) Hepatic abscess
3) Extraintestinal amebiasis

Mechanism of Action

- Metronidazole can penetrate protozoal and and most **anaerobic** bacterial cells, but not mammalian cells.

- In anaerobic organisms, the enzyme **pyruvate-ferredoxin oxidoreductase** reduces the drug.
- This reduction activates the drug, producing toxic metabolites.

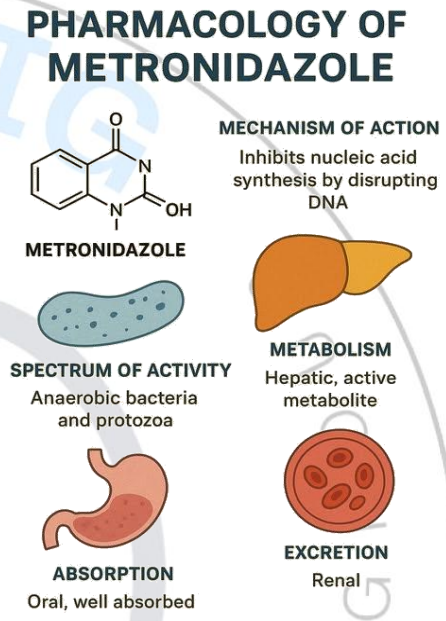
These metabolites:

1) **Disrupt DNA replication and transcription**
2) **Inhibit DNA repair**

Result → **death** of the parasite.

Important Note

Metronidazole kills trophozoites but does **NOT** kill cysts, therefore it **must be combined with a luminal amebicide** to completely eradicate infection.



Clinical Uses of Metronidazole

1) **Amebiasis**

Drug of choice for tissue infections caused by Entamoeba histolytica

2) **Giardiasis**

- Metronidazole is **the treatment of choice**.
- Treatment success rate is approximately 90%.
- Tinidazole is equally effective.

3) **Trichomoniasis**

- Metronidazole is also t**he treatment of choice**.

Typical regimen → Single oral dose of 2g.

Adverse effects

Common adverse effects:

1) Nausea
2) Headache
3) Dry mouth
4) Metallic taste

Less common adverse effects:

1) Vomiting
2) Diarrhea
3) Insomnia
4) Weakness
5) Dizziness

Rare adverse effects:

1) Pancreatitis
2) Severe central nervous system toxicity.

Precautions

Metronidazole should be a**voided in pregnant or nursing women whenever possible**, although clear congenital abnormalities have not been consistently associated with its use in humans.

Tinidazole

Tinidazole is similar to metronidazole.
Characteristics:

1) **Similar antimicrobial activity**
2) **Better toxicity profile**
3) **Can be administered as a single dose.**

It may be used as an alternative therapy for trichomoniasis.

Nifuratel

This is a broad-spectrum agent that can be used to treat bacterial, fungal and protozoal infections.
It can be used as an alternative to metronidazole and tinidazole to treat **trichomoniasis**.

Antimalarial drugs

Malaria is a mosquito-born disease of humans and other animals caused by parasitic protozoans belonging to the genus Plasmodium.

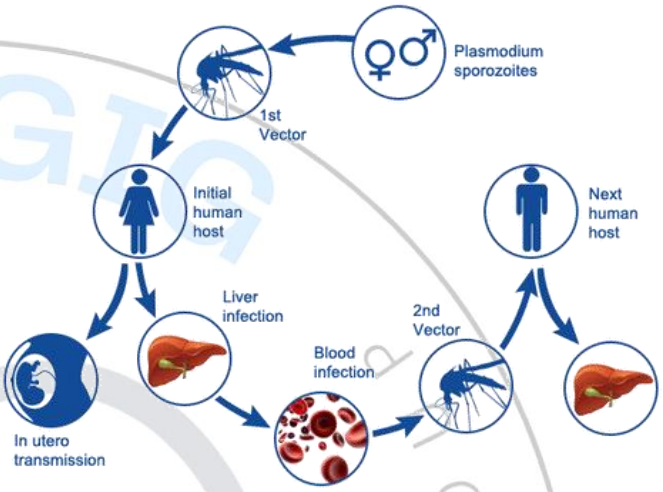
Malaria is transmitted by the bite of infected **female Anopheline** mosquitoes,

Life cycle of malaria

1) From the saliva of the mosquito, the parasite enters the blood circulation and travels to hepatocytes to multiply and grow.

2) The infection can remain asymptomatic for a period of 5-15 days, depending on the Plasmodium,

3) The parasite develops into **tissue schizonts** which rupture and release thousands of **merozoites** into the circulation.
4) The merozoites invade red blood cells where **mature schizonts** form.
5) Schizont-contating RBCs rupture releasing 6-32 merozoites which results cyclical febrile attacks every 2-3 days.



Clinical presentation

Presentation can range from mild disease to severe complicated.

1) Cyclical fever
2) Chills and sweats
3) Headaches
4) Nausea and vomiting
5) Body aches

Severe malaria can present with

1) Impaired consciousness
2) Seizures
3) Shock, which is a decrease in tissue perfusion.

Antimalarial drugs

1) Chroloquine

Mechanism of action

Inhibits the action of an enzyme called **heme polymerase**, which causes buildup of toxic heme in Plasmodium species.

Clinical use

- It is the most useful agent to terminate acute attacks
- Can be administered as oral, intravenous or intramuscular.

Adverse reactions

1) Nausea
2) Headaches
3) Teratogenic (results in physical or functional birth defect in the developing fetus).

- Plasmodium species can become **resistant** to this medications. Some areas are known to have **chloroquine-resistant** malaria.

2) Quinine

One of the oldest medications used to treat malaria.
It is a very **toxic** medication but still in use due to **lack of resistance**.

3) Artemisinin

A new medication derived from Sweet wormwood (الشيح).

Mechanism of action

- It eliminates malaria during the blood stage by **generating free radicals** that exert a toxic effect.

4) Doxycycline

A medication that is used to treat various bacterial and protozoal infections.
It can be used for:

1) **Prevention** (prophylaxis) for travelers to areas with **chloroquine-resistant malaria**.
2) **Treatment** in combination with other medications.

5) Pyrimethamine

An antiparasitic medication used to treat and prevent malaria.
It is rarely used alone due to resistance.

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Pharmacology

Anthelmintics

Written by: Noura Mohammad Alqaisi

Edited by: Rawan Fratekh

[Overview]

➔ **Outline anthelminthics:**

1) **Helminths (worms)**

2) **Anthelminthic medications overview**

3) **Treatments for infections caused by –----**
-Nematodes
-cestodes
-trematodes

[Helminths]

Helminths are large, multicellular parasitic worms that infect humans and animals.

➔ **Site of infection by helminths (worms):**
1) May stay only in the intestinal lumen.
2) May migrate through body tissues before settling.

➔ **Life cycle:**
1) **Simple:** egg deposition → development of an adult worm in one host.
2) **Complex:** requires intermediate host(s) and multiple stages that are metabolically distinct from each other, before developing into an adult.

➔ Pathogenic helminths are divided into:
1) Cestodes (flatworms)
2) Nematodes (round worms)
3) Trematodes (flukes)
4) Acanthocephala (thorny-headed worms)

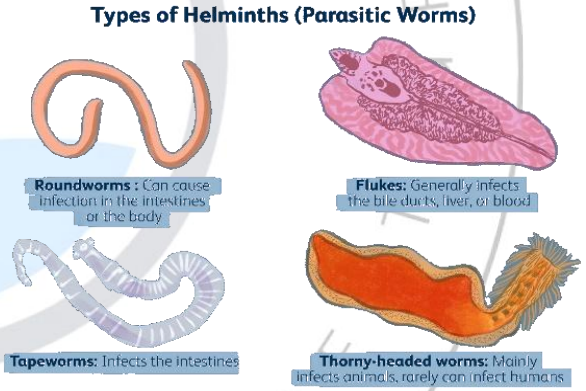
Cestodes (tapeworm) (Segments)

Flat, tape-like, segmented worms.
- **Length** ranges from millimeters to several meters.
- **Physical features:** Scolex (head) has **suckers and hooks** for attachment. The body is made of a **chain of segments** called strobila; each segment = proglottid. Adult worms live in the GI tract.
- **Organs:** No digestive system ➞ **absorb** nutrients through the body wall (Adult worms live in the GI tract)
- **Sex**: Usually, **hermaphrodites** (male & female organs in the same worm).
- **Life span**: about 5-25 years.

Nematodes (Roundworms)
- Long, narrow, thread-like body➞ name **"roundworm".**
- Many species are **microscopic**, but some parasites can be very large, e.g., one species may reach up to ~ 13 m.

Trematodes (flukes) (الديدان المثقوبة)
- Worldwide infections that cause different clinical diseases in humans.
- **Physical features**: Characteristic suckers for attachment **(**hence the name **flukes)**

Acanthocephala (Thorny-headed worms) (مشوكات الرأس)
- Parasites that live in **the gut of vertebrates** and spend their early life cycle in **invertebrates**.
- **Organs**: No mouth or digestive tract, adults absorb pre-digested nutrients directly through the body surface.



[Anthelminthic medications overview]

Anthelmintics are drugs that act either locally to expel worms from the GI tract or systemically to eradicate adult helminths or developmental forms that invade organs and tissues.

➔ **Main mechanisms of action of anthelmintics:**
1) Alter energy metabolism
2) Paralyze neuromuscular activity
3) Disrupt microtubules' function
4) Alter cell membrane permeability

[Treatments for infections caused by]

➔ ***Nematodes***

Piperazine (Vermizine)
Prolonged treatment and might need a purgative ملين

- **Structure**: contains a heterocyclic ring that lacks a carboxyl group.
- **Mechanism of action**: Works via **chloride-channel activation** (*chloride channel agonist on the parasitic muscle*) of the muscle membrane ➞ hyperpolarization ➞ **reversible flaccid paralysis of worms**, which are then expelled by intestinal peristalsis.

Diethylcarbamazine (DEC)

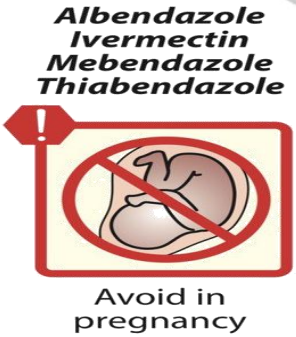
- **Mechanism of action**: **Alters arachidonic acid metabolism** → Prostaglandin production → Causes **capillary vasoconstriction and Immobilizes microfilariae**

Bendazoles (e.g., albendazole, mebendazole (Vermox)

- **Mechanism of action**: binds to tubulin and **inhibits microtubule polymerization**
- **Indications**:
  1) *Enterobius* (pinworm) → single dose, repeat after 3 weeks
  2) *Hookworm* → 2 tablets for 3 days
  3) *Ascaris*
  4) *Neurocysticercosis*

Ivermectin for hookworms (not mentioned in lecture slides)

Pyrantel pamoate (not mentioned in lecture slides)



➔ ***Cestodes (Tapeworms)***

Niclosamide

- **Mechanism of action**: **Inhibits anaerobic ATP production** (incorporation of inorganic phosphate into ATP) ➞ energy depletion ➞ **Damages scolex & proximal segments and leads to detachment** from the intestinal wall ➞ Worm removed by normal bowel peristalsis

Bendazoles (not mentioned in lecture slides)

Praziquantel (not mentioned in lecture slides)

➔ ***Trematodes (Flukes)***

Praziquantel (Biltricide)

- **Mechanism of action: increases Calcium permeability** in parasite so calcium accumulates within parasitic muscles ➞ this leads to **spastic paralysis** combined with **impaired motility** and **exposure of masked tegument antigens**, lipid-anchored protein, and actin, making the parasite susceptible to antibody & complement destruction.

QUICK TEST
Which of the following medications inhibits the phosphorylation of adenosine diphosphate?

A. Albendazole
B. Mebendazole
C. Niclosamide
D. Praziquantel

Correct answer = C. Niclosamide inhibits the parasite's mitochondrial phosphorylation of adenosine diphosphate (ADP), which produces usable energy in the form of adenosine triphosphate (ATP).