Antidiarrheal Agents

- Should not be used in patients with **bloody diarrhea**, **high fever**, or **systemic toxicity** [contraindicated in these patients] because of the **risk of worsening the underlying condition**.
- **Diarrhea** causes **loss of fluids and electrolytes** so we have to be careful while using the antidiarrheal agents.
- Used to control chronic diarrhea caused by irritable bowel syndrome (IBS) or inflammatory bowel disease.

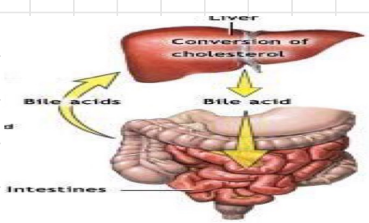
1. Opioid Agonists

- **Increase colonic transit time and fecal water absorption.**
- **decrease mass colonic movements** (causes constipation such as morphine and codeine; both used for treating diarrhea as antidiarrheal agents)
- **CNS effects** and potential for addiction **limit the usefulness** of most [as antidiarrheal agents]

Loperamide	Does not cross BBB, so No analgesic or addiction potential.
Diphenoxylate	Not analgesic in standard doses. Higher doses have CNS effects. Can cause dependence.
Lomotil	Combination of small amounts of atropine and small doses of diphenoxylate , contribute to the antidiarrheal action.

2. Bile Salt-Binding Resins

Malabsorption of bile salts cause diarrhea. (Crohn's disease or after surgical resection).
These drugs bind bile salts and decrease diarrhea caused by excess fecal bile acids.
Side effects : Can cause bloating, flatulence, constipation and fecal impaction.



Cholestyramine ☀ Colestipol ☀ Colesevelam

Both reduce absorption of drugs and fat.

3. Octreotide

Synthetic octapeptide with actions similar to **somatostatin**.

What is somatostatin? a hormone, an A14 amino acid peptide released in the GIT, pancreas as well as from the hypothalamus.
It has many actions such as:
1. inhibiting the release of many hormones (gastrin, cholecystokinin, glucagon, growth hormone, insulin, secretin pancreatic polypeptide, vasoactive intestinal peptide and 5- HT (Serotonin or 5-hydroxytryptamine).
2. reduction of intestinal fluid and pancreatic secretions.
3. slowing GIT motility and gallbladder contraction
4. contracting blood vessels.
5. Inhibits secretion of some anterior pituitary hormones

Clinical Uses:

1- Inhibition of endocrine tumor effects:
Carcinoid and VIPoma (neuroendocrine tumors that secrete vasoactive intestinal polypeptide (VIP)) can cause secretory diarrhea, flushing and wheezing.
2- Diarrhea due to vagotomy or dumping syndrome (ingested foods bypass the stomach too rapidly) or short bowel syndrome and AIDS.
3- To stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma (a disease affecting the skin and other organs that is one of the autoimmune rheumatic diseases)
4- It inhibits pancreatic secretion, so used in patients with pancreatic fistula (leakage of pancreatic secretions from damaged pancreatic ducts).
5- treatment of pituitary tumors (e.g., acromegaly)
6- Sometimes used in gastrointestinal bleeding.

Adverse Effects:

- Impaired pancreatic secretion may cause steatorrhea which can lead to fat-soluble vitamin deficiency.
- Nausea, abdominal pain, flatulence, and diarrhea.
- Formation of sludge or gallstones, due to inhibition of gallbladder contractility and fat absorption.
- Hyper or hypoglycemia due to hormonal imbalance.
- Hypothyroidism.
- Bradycardia.

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.

1- Antispasmodics (Anticholinergics)

Dicylomine and Hyoscyamine .

- Block muscarinic receptors in the enteric plexus and on smooth muscle.
- Their efficacy for relief of abdominal symptoms (are used to relieve the spasm or abdominal pain) has never been convincingly demonstrated.
- Low doses cause minimal autonomic effects.
- Higher doses [effective doses] cause anticholinergic effects [side effects] , including dry mouth, visual disturbances, urinary retention, and constipation.

For these reasons, antispasmodics are infrequently" less" used.

Alosetron	Potent & selective antagonist of the 5-HT3 receptor.	Rapidly absorbed, half-life of 1.5h but has a much longer duration of effect .	Restricted to women with severe diarrhea- predominant IBS not responding to conventional therapies. Its efficacy in men has not been established.
Prucalopride	High-affinity 5-HT4 agonist.	No cardiovascular toxicity .	Used for the treatment of chronic constipation in women.

2- Chloride Channel Activator

Chloride channels are critical to the digestive process because they promote fluid to release into the intestines.

Lubiprostone

- PG analog stimulates type 2 chloride channel (CIC-2) in the small intestine, this increases liquid secretion in the intestine which stimulates intestinal motility .
movement within 24 hours of taking one dose.
- Used in the treatment of chronic constipation.
- Approved for the treatment of women with IBS with predominant constipation.
- Its efficacy for men with IBS is unproven.
- Should be avoided in women of child-bearing age.
- side effects include Nausea (30%) due to delayed gastric emptying.

3- Antiemetic Agents

Nausea and vomiting may be manifestations of a wide variety of conditions, including:

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

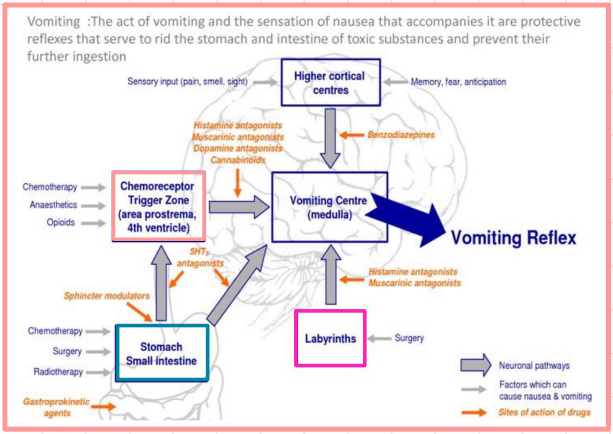
Pathophysiology

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.
** The act of vomiting includes many actions: contraction of the diaphragm to push the opening of the esophagus sphincter in order for the contents to go up, proceeding with nausea and increased secretions so lots of coordination occurring in the vomiting center. **

Vomiting center contains high concentrations of:

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

So we use their antagonists



- Chemoreceptor trigger zone stimulation by chemotherapy, anesthetics and opioids leads to the activation of the vomiting center, and so initiates the vomiting reflex.
- Labyrinths in ear surgery can also cause vomiting.
- Stomach and small intestines irritation, chemotherapy, surgery and radiotherapy may also cause vomiting

1- Serotonin 5-HT3 Antagonists.

Ondansetron Granisetron

Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.
Prevent emesis due to vagal stimulation and chemotherapy. (the stimulation of the peripheral 5-HT3 receptors on the sensory vagal nerve can cause nausea and vomiting)
Other emetic stimuli such as motion sickness are poorly controlled.(better controlled by antihistamine drugs)

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.

2- Neurokinin 1 Receptor (NK1) Antagonists

Block central NK1 receptors in the area postrema (the chemoreceptor trigger zone)

Aprepitant

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

Cannabinoids [cannabis weed derived] Dronabinol, Nabilone (Psychoactive agents).

Used for chemotherapy-induced vomiting. Mechanisms for these effects are not understood.

Adverse effects

Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.

3- Antipsychotic drugs

Prochlorperazine
Promethazine
Droperidol

→ (dopamine antagonists)

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

Benzodiazepines "Lorazepam & Diazepam" (valium)

Reduce anticipatory vomiting caused by anxiety.
(when a patient is going to have a major surgery, they anticipate pain and this can cause nausea and vomiting, so these drugs prevent this effect)

4- H1 Antihistamines & Anticholinergic Drugs

Particularly useful in motion sickness.

Side effects :

May cause dizziness, sedation, confusion, dry mouth, cycloplegia, and urinary retention.

Diphenhydramine, Dimenhydrinate

Have significant anticholinergic properties.

Meclizine

Minimal anticholinergic properties and less sedating.
Used for the prevention of motion sickness and the treatment of vertigo due to labyrinth dysfunction.

Hyoscine (scopolamine)

Very high incidence of anticholinergic effects.
It is better tolerated as a transdermal patch.

Drugs Used to Treat Inflammatory Bowel Disease

Introduction.

Inflammatory bowel disease (IBD): Ulcerative colitis & Crohn's disease.
Etiology & pathogenesis are unknown.

Crohn's disease.	Ulcerative colitis
can affect any part of the GIT. Most cases start in the terminal ileum.	restricted to the colon and the rectum.
affects the whole bowel wall.	restricted to the mucosa

Both present with extra- intestinal manifestations (such as liver problems, arthritis, skin manifestations and eye problems) in different proportions.

1) Aminosalicylates

5-aminosalicylic acid (5-ASA)

* Aminosalicylates work topically (not systemically) so it has to reach the infected area in areas of diseased gastrointestinal mucosa.
* Up to 80% of unformulated 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon.
(leaving only 20% to get to the infected area and start its work)
*A number of formulations deliver 5-ASA to various distal segments of the small bowel or the colon.

** Azo Compounds **

Sulfasalazine, Balsalazide, Olsalazine

- 5-ASA bound by an azo (N=N) bond to an inert compound or to another 5-ASA molecule.
- The azo structure markedly reduces absorption of the parent drug from the small intestine. (this is beneficial because all the side effects comes from the absorbed portion of the drug).
- In the terminal ileum and colon, resident bacteria cleave the azo bond by an azoreductase enzyme, releasing 5-ASA to work on the affected area.

** Mesalamine Compounds **

Pentasa

Timed-release microgranules that release 5-ASA gradually throughout certain segments of the small intestine .

Asacol

5-ASA coated in a pH-sensitive resin that dissolves at the pH of the distal ileum and proximal colon).

5-ASA also delivered as:

Enema (Rowasa)

Suppositories (Canasa).

The mechanism of action of 5-ASA is not certain but Several ones were proposed, including:

1-Inhibition of cytokine synthesis
2-Inhibition of prostaglandin and leukotriene synthesis 3-Free radical scavenging
4-Immunosuppressive activity
**ASA inhibits both T-cell proliferation and subsequent activation and differentiation.
5- Impairment of white cell adhesion and function

Clinical Uses

5-ASA drugs are first-line agents for treatment of mild to moderate active ulcerative colitis. Their efficacy in Crohn's disease is unproven, although used as first-line therapy for mild to moderate disease involving the colon or distal ileum.

Adverse Effects:

Due to systemic absorption; most severe especially in slow acetylators.
Nausea, headache, arthralgia, myalgia, bone marrow suppression, and malaise.
Also, allergic reactions, oligospermia "low sperm count", and folate deficiency.

2) Glucocorticoids

-Inhibit production of inflammatory cytokines and chemokines.
-Reduce expression of inflammatory cell adhesion molecules.
- inhibit gene transcription of nitric oxide synthase, phospholipase A2, cyclooxygenase-2, and NF- B.

Clinical Uses

Moderate to severe active IBD. Not useful for maintenance.
For maintenance; a long time treatment of glucocorticoids is required, we can't do that due to the numerous side effects .

Prednisolone Orally or IV.
Hydrocortisone Rectally for rectal and sigmoid involvement.
Budesonide
A controlled-release oral formulation ,releases the drug in the distal ileum and colon for ileal and proximal colon involvement

3) Antimetabolites

1❦ Azathioprim, 6-Mercaotopurine.

- Are purine analogs; which produce thioguanine nucleotides (Active form).
- They're Immunosuppressants.
- Inhibit purine nucleotide metabolism and DNA synthesis

and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis.

Clinical Use:

- Onset delayed for 17 weeks. " we start treatment with other drugs alongside these antimetabolites cause their effect will start after 17 weeks"
- Used in induction and maintenance of remission. Allow dose reduction or elimination of steroids.

Adverse Effects:

- Nausea, vomiting, bone marrow suppression, hepatic toxicity and allergic reactions(fever, rash, pancreatitis, diarrhea and hepatitis).
- Allopurinol increases levels of the drugs.

2❦ Methotrexate

Antimetabolite,Used incancerchemotherapy,rheumatoidarthritisand psoriasis.
Mechanism of action:
Inhibition of dihydrofolate reductase enzyme which is important in the synthesis of thymidine and purines.
- At high doses it inhibits cellular proliferation.
- At low doses used in IBD, it interferes with the inflammatory actions of interleukin-1, stimulates adenosine release, apoptosis and death of activated T lymphocytes.

Uses

Induction and maintenance of remissions of Crohn's Disease.

Adverse effects:

At high doses, can cause:
* bone marrow depression, megaloblastic anemia, alopecia and mucositis.
* Renal insufficiency may increase risk of hepatic accumulation and toxicity.
* Side effects counteracted by folate supplementation.

4) Anti-Tumor Necrosis Factor Therapy

TNF-α is one of the principal cytokines mediating the TH1 (helper T cell type 1) immune response which is a characteristic of Crohn's disease.

Infliximab

- A chimeric immunoglobulin (25% mouse, 75% human) that binds to and neutralizes TNF-α .
- Infliximab binds to both soluble & transmembrane forms of TNF- αand inhibits their ability to bind to TNF receptors and may cause lysis of these cells.
- Given by IV infusion.
- Half life 8-10 days with persistence of antibodies in plasma for 8-12 weeks.
- Used in moderate to severe Crohn's disease.
- Also used in acute and chronic treatment of patients with refractory ulcerative colitis.

Response might be lost due to development of antibodies to infliximab. "the body produces antibodies against this drug"

Side Effects:

Acute:

fever, chills, urticaria, or even anaphylaxis Delayed "appears 1-3 weeks after treatment": serum sickness-like reactions may develop after infliximab infusion, but lupus-like syndrome occurs only rarely.

- Antibodies to infliximab can decrease its clinical efficacy. Therapy is associated with increased incidence of respiratory infections; reactivation of TB.
- Infliximab also is contraindicated in patients with severe congestive heart failure.

Adalimumab

Fully humanized IgG antibody, given SC -subcutaneously-.

Certolizumab

Polyethylene glycol Fab fragment of humanized anti- TNF-α, also given SC.

- Both these drugs have immunogenicity that appears to be less of a problem than that associated with infliximab.

Natalizumab

Humanized IgG4 monoclonal antibody against the cell adhesion molecule α4-integrin subunit. Prevents binding of several integrins on circulating inflammatory cells to vascular adhesion molecules.

Used for patients with moderate to severe Crohn's disease who have failed other therapies. Given by IV infusion every 4 weeks, and patients should not be on other immune suppressants to prevent the risk of progressive multifocal leukoencephalopathy (rare and usually fatal viral disease)

Adverse effects include acute infusion reactions & a small risk of opportunistic infections.

Pancreatic Enzyme Supplements

Contain a mixture of amylase, lipase, and proteases.
Used to treat pancreatic enzyme insufficiency.

Pancrelipase.

Available in both non-enteric-coated (given with acid suppression therapy) & enteric-coated preparations.
Administered with each meal and snack.
Excessive doses may cause diarrhea and abdominal pain.
The high purine content of pancreas extracts may lead to hyperuricosuria and renal stones. (high uric acid concentration causes its perception forming renal stones).

Drugs Used to Treat Variceal Hemorrhage

- Portal hypertension commonly occurs as a consequence of Chronic liver disease.
- Portal hypertension is caused by increased blood flow within the portal venous system & increased resistance to portal flow within the liver. "leading to blood accumulation in veins "balloon shaped", walls of the veins are thin so they may rupture leading to hemorrhage"
- Splanchnic blood flow is increased in patients with cirrhosis.
- The extra blood flow causes the veins in the esophagus to balloon outward.
- Varices can rupture, leading to massive upper GI bleeding.

1- Somatostatin & Octreotide

- In patients with cirrhosis and portal hypertension, intravenous somatostatin or octreotide reduces portal blood flow and variceal pressures.
- They inhibit the release of glucagon and other gut peptides that alter mesenteric blood flow.
- They promote initial homeostasis from bleeding esophageal varices.
- They are generally administered for 3-5 days.

2- Beta-Receptor-Blocking Drugs

- Beta-receptor antagonists reduce portal venous pressures via a decrease in portal venous inflow.
- This decrease is due to a decrease in cardiac output (β1blockade) and to splanchnic vasoconstriction (β2blockade) caused by the unopposed effect of systemic catecholamines on alpha a receptors.
- Thus, nonselective blockers such as propranolol and nadolol are more effective than selective β1blockers in reducing portal pressures.
- Nonselective β blockers significantly reduce the rate of recurrent bleeding. "they have mild, sudden effect and are well tolerated which makes them excellent drugs."

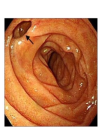
Vasopressin (antidiuretic hormone)

The doctor did not mention or read these two slides

Is a potent arterial vasoconstrictor.

IV infusion causes splanchnic arterial vasoconstriction that leads to reduced splanchnic perfusion and lowered portal venous pressures.

Vasopressin was commonly used to treat acute variceal hemorrhage. Because of its high adverse-effect profile, it is no longer used for this purpose.



Patients with acute gastrointestinal bleeding from small bowel or large bowel vascular **ectasias** or **diverticulosis**, vasopressin may be infused—to promote vasospasm—into one of the branches of the superior or inferior mesenteric artery through an angiographically placed catheter.

Adverse effects:

Are common. hypertension, myocardial ischemia or infarction, or mesenteric infarction.

Other common adverse effects are nausea, abdominal cramps, and diarrhea (due to intestinal hyperactivity).

vasopressin promotes retention of free water, which can lead to hyponatremia, fluid retention, and pulmonary edema.

Terlipressin is a vasopressin analog that have similar efficacy to vasopressin with fewer adverse effects.