Drugs to Treat Gastrointestinal Disorders
OBJECTIVES

• Understand the physiology of gastric acid secretion and gastric defense

• Knowledge of what causes peptic ulcer diseases and the clinical treatments for it

• Knowledge of what causes constipation and how it is treated

• Understand the causes of diarrhea and the clinical treatments for it
Acid-Peptic Disease

- Gastroesophageal Reflux Disease (GERD)
- Peptic ulcer (gastric and duodenal)
- Stress-related mucosal injury

Imbalance between

- *Aggressive* factors (acid, pepsin, bile)
- *Defensive* factors of the GI mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow and the process of regeneration after cellular injury)
Physiology of Acid Secretion

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**Physiology of Acid Secretion**

- **Gastric acid secretion**: multiple central and peripheral factors → common endpoint → secretion of $H^+$ by parietal cells.

- Neuronal (acetylcholine - M3), paracrine (histamine – H2) and endocrine (gastrin – CCK2) → on the basolateral membrane of **parietal cells** in the body and fundus of the stomach and regulate gastric acid secretion

- **Ach** indirectly ↑ release of histamine from the **enterochromaffin-like** (ECL) cells in the fundus of the stomach and **gastrin** from the G cells of the gastric antrum.

- **Gastrin** stimulates acid secretion indirectly by inducing the release of histamine by ECL cells
**Gastric acid secretions - contd**

- **Ach** and gastrin → signal through GPCRs → $G_q$-PLC-IP$_3$-Ca$^{2+}$ pathway in parietal cells.

- **Histamine** → paracrine mediator, diffusing from its site of release (ECL cells) to nearby **parietal cells** and activates **$H_2$ receptors** (GPCR that activates $G_s$-adenylyl cyclase-cAMP-PKA pathway).

- In **parietal cells**, the cAMP and the Ca$^{2+}$-dependent pathways activate **H$^+$,K$^+$ ATPase** (the proton pump), which exchanges hydrogen and potassium ion across the parietal cell membrane.

Note: This pump generates the largest known ion gradients in vertebrates, with an intracellular pH of about 7.3 and intracanalicular pH of about 0.8.
Gastric Defense

The extremely high concentration of H+ in the gastric lumen requires defense mechanisms to protect the esophagus and the stomach.

- **Lower esophageal sphincter** --- which prevents reflux of acidic gastric contents into the esophagus.

- The stomach protects itself from acid damage by a number of mechanisms that require **adequate mucosal blood flow**.

- *(i) secretion of a mucus layer* ------ protects gastric epithelial cells. Mucus production is stimulated by PGE$_2$ and PGI$_2$, which also directly inhibit gastric acid secretion by parietal cells.

- *(ii) secretion of bicarbonate ions* by superficial gastric epithelial cells. Bicarbonate neutralizes the acid in the region of the mucosal cells, thereby raising pH and preventing acid-mediated damage.
Gastric Defense


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Acid-Peptic Disease

- GERD
- Peptic ulcer (gastric and duodenal)
- Stress-related mucosal injury

**Imbalance between**

- *Aggressive* factors (acid, pepsin, bile)
- *Defensive* factors of the GI mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow and the process of regeneration after cellular injury)
PEPTIC ULCER DISEASE

• Disease can result from an increase in gastric acid secretion, pepsin activity, NSAIDs, *H. pylori* and/or a decrease in mucus, HCO$_3^-$ or PGs.

• Therapy is aimed at decreasing acid or promoting mucosal protection.
ANTACIDS

Pharmacological Properties

• One of the oldest approaches to treating gastric ulcers

• Antacids are weak bases, react with gastric acid (HCl). [The relative effectiveness is expressed as milliequivalents of acid-neutralizing capacity (defined as the quantity of 1N HCl, expressed in mEq, that can be brought to pH 3.5 within 15 minutes). According to FDA, antacids must have a neutralizing capacity of at least 5 mEq per dose.]

• * The basic group in the antacid neutralizes the acid to form water, carbon dioxide and chloride salts.
Antacids

• *Two general antacid categories
  – Systemic antacids – NaHCO₃ (baking soda, Alka Seltzer)

  – Non-systemic antacids – CaCO₃ (Tums), Al(OH)₃, Mg(OH)₂ (Milk of Magnesia), Al and Mg combinations (Mylanta, Gelusil)

• Added simethicone (a surfactant) decreases foaming and esophageal reflux.
Antacid-Adverse Effects

• Transient metabolic alkalosis – NaHCO$_3$
• Consider sodium levels in CHF.
• NaHCO$_3$ or CaCO$_3$: CO$_2$ released can cause belching, nausea, abdominal distention and flatulence.
• Ca$^{2+}$ may cause rebound acid secretion.
• GI Effects
  – Al(OH)$_3$ can cause constipation
  – Mg(OH)$_2$ can cause diarrhea
  – Net effect of combination agents (e.g. Gelusil, Maalox, etc.) depends on the relative amounts of the two agents.
Adverse Effects (cont.)

• Excessive use of Al and Mg antacids can lead to hypophosphatemia due to formation of insoluble metal phosphate salts.

• * In ↓ renal function, absorbed Al$^{3+}$ and Mg$^{2+}$ can lead to systemic toxicity.
Antacid-Drug Interactions

- Altered gastric or urinary pH may affect rate of absorption or excretion and the bioavailability of some drugs.

- Significant ↓ bioavailability – many factors: iron, theophylline, quinolone antibiotics, isoniazid, tetracycline and ketoconazole.

- Altered GI motility by Al$^{3+}$ or Mg$^{2+}$ or complex formation (Al) can alter absorption of some drugs.
ACID SECRETION INHIBITORS

• Two main pharmacological groups

  – Histamine H$_2$ Receptor Antagonists

  – Proton Pump Inhibitors
HISTAMINE H2 RECEPTOR ANTAGONISTS (H2RA)

- **Mechanism of Action:**
  - Competitive antagonists of histamine at H$_2$ receptors
  - ↓ volume of gastric juice and [H$^+$] content
  - ↓ pepsin secretion

- Include:
  - cimetidine (Tagamet),
  - ranitidine (Zantac),
  - nizatidine (Axid) and
  - famotidine (Pepcid)
• Cimetidine (prototype drug).

• Other agents are generally more potent than cimetidine and are longer acting.

• * Cimetidine, ranitidine and famotidine are biotransformed by the liver in varying amounts, while nizatidine is eliminated primarily by the kidney.

• All H2RA’s inhibit 60-70% of total 24-hr acid secretion

• Especially effective at inhibiting nocturnal acid secretion (Histamine dependent), but modest impact on meal-stimulated acid secretion (stimulated by gastrin, Ach and histamine)
**H2RA - Therapeutic Uses**

- **Gastric and Duodenal Ulcers** – Nocturnal acid suppression affords effective ulcer healing. If *H. pylori* is present then eradication of the infection should be instituted to reduce ulcer recurrence. If ulcer is caused due to aspirin or NSAIDs, the NSAIDs have to be discontinued.

- **Gastroesophageal Reflux Disease** – H2RA used for chronic management of heartburn. A major use for these drugs. For patients with erosive esophagitis (50% of patients with GERD), H2RA affords healing in <50% of patients.

- **Zollinger-Ellison syndrome** – Rare syndrome where gastrin-producing tumor ↑ HCl secretion.

- **Acute Stress Ulcers** – associated with significant physical trauma in high-risk patients in ICUs. (continuous iv H2 antagonists)
H2RA
Adverse Effects

• The incidence of adverse effects are low and generally minor.

• Most common adverse effects (1-3%) are headache, itching, rashes, lethargy and confusion. The last two are seen mostly in elderly patients or patients with renal impairment.
**H2RA**

* **Drug Interactions**

- Similar to antacids (increasing pH), interactions due to altered gastric acid secretion.

- * Cimetidine – inhibits CYP450 and alters the biotransformation rate of many drugs. May increase toxicity of second drug if dose adjustments are not made.

- Other H2RAs have no effect on hepatic biotransformation of other drugs.
**PROTON PUMP INHIBITORS**

- *Mechanism of action: PPIs irreversibly inhibit the H⁺/K⁺-ATPase in parietal cells to ↓ basal and stimulated gastric acid secretion (>90%).

- Include:
  - omeprazole (Prilosec),
  - esomeprazole (Nexium),
  - lansoprazole (Prevacid),
  - rabeprazole & pantoprazole

- PPI’s are prodrugs and require activation in acidic environment--------→
**PPIs – Therapeutic Uses**

- **Peptic ulcers** – more rapid symptom relief, faster ulcer healing compared to H2RA, [eradicate *H. pylori* infection if present to reduce recurrence of ulcer formation].

- **GERD**: most effective for treatment of nonerosive and erosive reflux disease. [PPI provides symptomatic relief in 70-80% GERD patients compared to 50-60% relief by H2RA.]

- **Zollinger-Ellison syndrome**

- **Lansoprazole** is FDA approved for treatment and prevention of recurrence of NSAID-associated gastric ulcers in patients with continued NSAID use.
PPIs – Adverse Effects

• Generally well tolerated

• Adverse effects at 1.5-3% incidence include mainly GI effects (nausea, diarrhea, flatulence) and some CNS effects (headache, dizziness).

• Prolonged use of prescription strength PPI could lead to CKD and end-stage renal disease

• Gastric cancers have been observed in animals. Humans?
PPIs – *Drug Interactions

- Interactions due to altered gastric acid secretion similar to antacids and H2RA.

- Omeprazole and esomeprazole— inhibits CYP450s (Cyp2c19*)
- Can increase serum levels of drugs metabolized by Cypc19 such as diazepam (Valium)
- Omeprazole and esomeprazole can inhibit conversion of antiplatelet drug clopidogrel (plavix and generics) to its active form (patients taking clopidogrel use other PPIs such as lansoprazole etc).

- *Cyp2c19 polymorphic variants have been identified. Asians compared to Caucasians or African Americans have the Cyp2c19 genotype that correlates with slow metabolism of PPIs (23% vs 3% respectively), which may contribute to heightened efficacy and/or low toxicity in this group.
AGENTS THAT ENHANCE MUCOSAL DEFENSE:

DRUGS THAT PROMOTE MUCOSAL PROTECTION

- Misoprostol
- Sucralfate
- Bismuth Compounds
- Metoclopramide (LES)
Misoprostol (CYTOTEC)

- A stable methyl analog of PGE$_1$
- Biological effects include: ↓ acid secretion, ↑ mucous and HCO$_3^-$ secretion

- Therapeutic uses:
  - prevention of peptic (gastric) ulcer disease related to NSAID administration in high risk patients.
  - Less effective than H2RA for other types of peptic ulcer disease.
Misoprostol – Adverse Effects

• GI effects – cramping, diarrhea, and nausea are the most common side effects.

• Can cause clinical exacerbations of IBD (diarrhea) and should be avoided in patients with this disorder.

• Promotes uterine contractions

• Contraindicated in pregnancy.
**Sucralfate**

- In the presence of acid-induced damage, pepsin-mediated hydrolysis of mucosal proteins contributes to mucosal erosion and ulcerations.

- A sulfated sucrose and polyaluminium hydroxide complex (Carafate).

- *Mechanism of action:* At pH < 4, sucralfate forms polymers/cross-links to form a sticky gel that adheres to GI epithelial cells and ulcer craters. A protective barrier against acid (inhibits hydrolysis of mucosal proteins by pepsin) and stimulates local PGE2 production.

- **Adverse effects:** Released Al $^{3+}$ may cause constipation.
- *Antagonized by agents that ↑ gastric pH.*
Bismuth Compounds

• Colloidal bismuth subcitrate (GI ulcers) and bismuth subsalicylate- PEPTO-BISMOL (ulcers and heartburn).

• *Mechanism of action: Bismuth probably coats ulcer craters, ↑ mucus and HCO₃⁻ secretion, inhibits pepsin activity and is antibacterial toward H. pylori. Healing rate of ulcers better with H2RA.

• Adverse effects: Can darken oral cavity and stool (bismuth sulfide from reaction with bacterial H₂S).
**Metoclopramide**

- *Metoclopramide* (Metozolv ODT, Regalan) has combined cholinergic agonist and dopamine antagonist (D2 receptor) activity. A prokinetic (gut motor function) agent.

- *Mechanism of action:* ↑ esophageal clearance, ↑ LES pressure and gastric emptying. Net effect is to ↓ reflux.

- Therapeutic Use: Tx of symptomatic GERD but are not effective in patients with erosive esophagitis. (it is also used in patients with diabetic gastroparesis)

- Adverse effects: hyperprolactinemia, CNS effects, tardive dyskinesia

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Feb 2009: The U.S. Food and Drug Administration (FDA) required for manufacturers to add a boxed warning to the metoclopramide prescribing information related to a link between chronic use and the development of **tardive dyskinesia** (involuntary and repetitive movements of the body).
HELICOBACTER PYLORI

• *H. pylori* – a gram-negative rod that grows on the luminal side of the gastric epithelium.

• At least 70-90% of patients with peptic ulcer have *H. pylori* in their GI tract.

• Impaired production of somatostatin by Δ cells, inhibition of gastrin production, leading to ↑ acid production and ↓ bicarbonate production

• Single agent therapy not effective in eradicating the microorganism.

Warren and Marshall, 2005
Eradication of H. pylori

- Treatment requires multi-agent therapy if patient tests positive for *H. pylori*.
- Triple therapy or quadruple therapy x 14 days
  - **Triple Therapy** x 14 days: [PPI + clarithromycin + (metronidazole or amoxicillin)] twice a day
  - **Quadruple Therapy*** x 14 days: PPI twice a day + metronidazole three times daily + (bismuth subsalicylate + tetracycline four times daily).
    
    Or
    
    H2RA twice a day + (bismuth subsalicylate + metronidazole + tetracycline four times daily).

* In areas with a high frequency of resistance to clarithromycin and metronidazole
GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Also known as heartburn, affects 10% of the US population.

- Antacids (neutralize gastric acid).

- H2RA and PPIs inhibit acid secretion and are preferred if problems persist with the use of OTC antacids.
Severity of GERD

**Stage I**
Sporadic uncomplicated heartburn, often in setting of known precipitating factor. Often not the chief complaint. Less than 2-3 episodes per week. No additional symptoms.

**Medical Management**
Lifestyle modification, including diet, positional changes, weight loss, etc. Antacids and/or histamine H₂-receptor antagonists as needed.

**Stage II**
Frequent symptoms, with or without esophagitis. Greater than 2-3 episodes per week.

Proton pump inhibitors more effective than histamine H₂-receptor antagonists.

**Stage III**
Chronic, unrelenting symptoms; immediate relapse off therapy. Esophageal complications (e.g., stricture, Barrett's metaplasia)

Proton pump inhibitor either once or twice daily.


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The success of acid-suppressing agents in a variety of conditions is critically dependent upon their ability to keep intragastric pH above a certain target, generally pH 3 to 5.

Data shows the effects of PPI (given once daily) and H2RA (given twice daily) in elevating gastric pH to the target ranges.
CONSTIPATION

- Constipation is characterized by dry stools that are often voided with excessive straining. Frequency of defecation is also reduced.

- Can be caused by a wide range of causes, including drugs, stress, diet, and diseases of the GI tract.
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<th>Table 38–1</th>
<th>Some Agents Causing Constipation</th>
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<td>Iron</td>
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<td>Laxatives (used chronically)</td>
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<td>Monoamine oxidase inhibitors</td>
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<td>Octreotide</td>
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<td>Opioids</td>
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<td>Phenothiazines (anticholinergic effect)</td>
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<td>Polystyrene resins</td>
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<td>Propranolol</td>
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<td>Tricyclic antidepressants (anticholinergic effect)</td>
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<td>Verapamil</td>
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</table>
Laxatives - Actions

Laxatives generally act in one of the following ways:

1. Luminally active agents (enhancing retention of intraluminal fluid by hydrophilic or osmotic mechanisms)
   a. Hydrophilic colloids; bulk-forming agents (fiber such as bran, psyllium, etc.)
   b. Osmotic agents (nonabsorbable inorganic salts or sugars)
   c. Stool-wetting agents (surfactants) and emollients (docusate, mineral oil)

2. Nonspecific stimulants or irritants (decreasing net absorption of fluid by effects on small- and large bowel fluid and electrolyte transport and motility)
   a. Diphenylmethanes (bisacodyl)
   b. Anthraquinones (senna and cascara)
   c. Castor oil (ricinoleic acid)

3. Prokinetic agents (acting primarily on motility by either inhibiting segmenting contractions or stimulating propulsive contractions)
   a. 5-HT4 receptor agonists
   b. Opioid receptor antagonists

Note: Laxation: evacuation of formed fecal material from the rectum
       Catharsis: evacuation of unformed, usually watery fecal material from the entire colon.
Bulk-forming laxatives  
(Dietary Fibers)

• DF are bulk-forming agents that include:
  natural: bran, whole grains, psyllium preparations (isabgol-METAMUCIL),
  synthetic: methylcellulose (CITRUCCEL) and calcium polycarbophil (FIBERCON).

• * They absorb water to soften the stool and increase bulk.

• * Generally well tolerated, but intestinal obstruction and impaction can occur.
Osmotic Laxatives

- NOTE: The colon can neither concentrate or dilute fecal fluid: fecal water is isotonic throughout the colon.
- Osmotic laxatives are soluble but non-absorbable compounds that increase stool liquidity.

- **SALINE laxatives** include **magnesium salts** (hydroxide, sulfate, citrate) and **phosphate salts** (oral or rectal).
  - * Act via their osmotic pressure to retain water in the colon which stimulates peristalsis.

- **OTHER laxatives** include **lactulose and mannitol** (non-absorbable sugars).
  - Are hydrolyzed in colon to short-chain fatty acids
  - * Osmotic effects retain water in the colon and soften stools and also promote colonic propulsive motility.
Stimulant & Surfactant Laxatives

• **STIMULANT** laxatives include bisacodyl (DULCOLAX). OTC preparations are popular.
  • *Act by stimulating mucosal water and electrolyte secretion.*

• **SURFACTANT** laxatives include the docusates, and castor oil.
  • *Lower the surface tension of the stool to allow mixing of aqueous and fatty substances thus softening the stool and easier defecation*
  • stimulate mucosal water and electrolyte secretion and alter intestinal mucosal permeability
  • *Docusates are mainly wetting and emulsifying agents that help soften the stool.*
* **Castor Oil**

The oil of the castor bean contains a triglyceride ester of ricinoleic acid.

- * Castor oil (PURGE, NEOLOID) is cleaved to ricinoleic acid in the SI and can produce a purging effect with semi-fluid stools in 1-6 hours. Can be days before a normal defecation.

- * Ricinoleic acid is an anionic surfactant that ↓ net absorption of fluid/electrolytes and stimulates peristalsis.

* **Mineral Oil**

- A mixture of aliphatic hydrocarbons obtained from petroleum.

- A non-absorbed oil lubricant that softens the stool.

- * Can decrease the absorption of fat-soluble vitamins.

- If aspirated, lipid pneumononitis can occur.
## Classification and Comparison of Representative Laxatives

<table>
<thead>
<tr>
<th>Softening of Feces, 1 to 3 Days</th>
<th>Soft or Semifluid Stool, 6 to 8 Hours</th>
<th>Watery Evacuation, 1 to 3 Hours</th>
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<tr>
<td><strong>Bulk-forming laxatives</strong></td>
<td><strong>Stimulant laxatives</strong></td>
<td><strong>Osmotic laxatives</strong>*</td>
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<tr>
<td>Bran</td>
<td>Diphenylmethane derivatives</td>
<td>Sodium phosphates</td>
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<td>Psyllium preparations</td>
<td>Phenolphthalein</td>
<td>Magnesium sulfate</td>
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<td>Methylcellulose</td>
<td>Bisacodyl</td>
<td>Milk of magnesia</td>
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<tr>
<td>Calcium polycarbophil</td>
<td>Anthraquinone derivatives</td>
<td>Magnesium citrate</td>
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<tr>
<td><strong>Surfactant laxatives</strong></td>
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<td><strong>Castor oil</strong></td>
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<tr>
<td>Docusates</td>
<td>Senna</td>
<td></td>
</tr>
<tr>
<td>Poloxamers</td>
<td>Cascara sagrada</td>
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<tr>
<td>Lactulose</td>
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</tbody>
</table>

*Employed in high dosage for rapid cathartic effect and in lower dosage for laxative effect.*
Other FDA approved Drugs for Chronic Idiopathic Constipation and Irritable Bowel Syndrome with Constipation

Lubiprostone (Amitiza) (2012)

- A metabolite of prostaglandin E1
- Opens chloride channels on the luminal surface of the GI epithelium
- Stimulates intestinal secretion of fluid and electrolytes
- Accelerates stool transit time
- Modestly effective also in treating opioid-induced constipation

Linaclotide (Linzess) (2013)

- Guanylate cyclase-C receptor agonist (14-amino acid synthetic peptide)
- Activates Guanylate cyclase C receptors on the luminal surface of the intestinal epithelium, increasing cGMP within intestinal epithelial cells
- Results in activation of CFTR ion channel, increasing the secretion of chloride and bicarbonate ions into the intestinal lumen
- Increases intraluminal fluid and accelerates intestinal transit
- Adverse effects: diarrhea, abdominal pain, flatulence; (black box warning against use in patients <18 years due to deaths in young mice.)
Opioid Induced Constipation

- **Naloxegol** (Movantik), a pegylated derivative of the opioid antagonist naloxone
- Only oral opioid antagonist approved by FDA in 2014
- Mechanism: Opioids exert their analgesic effect by stimulating mu receptors in the CNS, but also stimulate peripheral mu receptors in the GI tract leading to decreased muscle contractility, inhibition of water and electrolyte secretion and increased rectal sphincter tone.
- Naloxegel is a peripheral mu-opioid receptor antagonist. Pegylation reduces ability to cross BBB and makes it a substrate of the efflux transporter P-glycoprotein.
- Adverse effects- dose related: abdominal pain, diarrhea, nausea, flatulence and vomiting
Uses and Abuses of Laxatives

• Uses: maintain soft feces, prevent straining during defecation and evacuation of the bowel, before surgery or diagnostic procedures.

• Contraindicated in patients with cramps, colic, nausea, vomiting, undiagnosed pain, or symptoms of appendicitis.

• Abuses: The laxative habit.
Other uses of Laxatives

• Frequently employed before surgical, radiological and endoscopic procedures – where empty colon is desirable

• Enemas and suppositories: are commonly employed either by themselves or as adjuncts to bowel preparations to empty distal colon or rectum of retained solid material
DIARRHEA

• “Too rapid evacuation of too fluid stools”

• Characterized by watery stools and can be associated with an ↑ frequency of defecation (> 3x/day).

• Caused by microorganisms (e.g. *E. coli*), drugs or toxicants.

• Excessive water and electrolyte loss can lead to dehydration and electrolyte imbalance.
Table 38-2

Some Agents Causing Diarrhea

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Adrenergic neuron blocking agents (reserpine, guanethidine)</td>
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<tr>
<td>Antimicrobials (e.g., sulfonamides, tetracyclines, most broad-spectrum agents)</td>
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<td>Bile acids</td>
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<td>Carcinoid tumor secretions (e.g., 5-hydroxytryptamine, vasoactive intestinal peptide, substance P)</td>
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<td>Cholinergic agonists and cholinesterase inhibitors</td>
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<td>Fatty acids</td>
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<tr>
<td>Osmotic and stimulant laxatives</td>
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<tr>
<td>Prokinetic agents (metoclopramide, domperidone, cisapride)</td>
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<tr>
<td>Prostaglandins</td>
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<td>Quinidine</td>
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</table>
Treatment of Diarrhea

- Nonspecific antidiarrheals – aim is to prevent dehydration and electrolyte imbalances (oral rehydration therapy).

- If diarrhea is drug induced, then change the dose of the drug or change to a new drug.
Antidiarrheals - Opioids

*Mechanism of action:* Opioids stimulate the $\mu$ opioid receptors in the GI tract to:

- $\downarrow$ GI motility which $\uparrow$ transit time and absorption of water and salt.
- $\downarrow$ secretion of water and salt
Opioids (cont.)

• Agents include: diphenoxylate + atropine (Lomotil), diphenoxin (active metabolite of diphenoxylate) + atropine (motofen), and loperamide (Imodium).

• * Atropine affects GI motility and secretion, but side effects discourage abuse of the opioid preparation.

• * Loperamide is a piperidine butyramide derivative with a μ receptor activity, decreases intestinal motility and has anti-secretary activity

• * For mild diarrhea without fever or blood stools, loperamide (OTC) often relieves symptoms in <24 hours

• * For moderate-to-severe traveler’s diarrhea, loperamide + an appropriate antimicrobial (azithromycin) agent is preferred.

• Has poor CNS penetration.
Opioids – Adverse Effects

• Constipation

• With high doses of diphenoxylate + atropine, CNS effects can occur due to activation of central μ opioid receptors (opoid) and antimuscarinic effects (atropine).
Bismuth Subsalicylate

- * PEPTO-BISMOL - Used to treat mild-to-moderate traveler’s (infectious) diarrhea.

- Salicylate provides anti-inflammatory effects.

- Bismuth is anti-secretary, anti-inflammatory and antibacterial (used in the treatment of H. Pylori)

- Less effective than antibiotics

- Dark stools and black staining of the tongue
Somatostatin (SST) is a small peptide, produced by antral D cells.  

- inhibits gastric acid secretion. Acidification of gastric luminal pH<3 stimulates SST release, which in turn suppresses gastrin release in a negative feedback loop.

- SST-producing cells are decreased in patients with *H. pylori* infection and the consequent reduction of SSTs inhibitory effect may contribute to excess gastrin production.
Octreotide

- **Octreotide** (sandostatin): A synthetic analog of somatostatin

- Numerous effects on the GI tract including ↓ in GI endocrine secretions, intestinal fluid and HCO$_3^-$ secretion and smooth muscle contractility.

- Used to treat secretary diarrhea brought by hormone secreting tumors of the pancreas and GI tract

- chemotherapy-induced diarrhea, diarrhea associated with HIV-AIDS, diabetes-associated).
Inflammatoty Bowel Disease (IBD)

- Cause unknown; autoimmune disease?
- Crohn’s Disease: inflammation anywhere in the GI tract
- Ulcerative colitis: inflammation predominately in colon and rectum

- Pharmacology:
  - Involves drugs that belong to different therapeutic classes and have different non-specific mechanisms of anti-inflammatory action
  - Drugs chosen on the basis of disease severity, responsiveness and drug toxicity
Treatment options for IBD

- Treatment choice is predicted on the both severity of illness and responsiveness to therapy.
- **MILD**: 5-aminosalicylic acid (5-ASA-mesalamine) (UC or Crohn’s colitis),
  - Topical corticosteroids (UC)
  - Antibiotics (Crohn’s colitis or Crohn’s perianal disease)
  - Budesonide (glucocorticoid) (Crohn’s ileitis, UC- rectal foam)

- **MODERATE**: (the patients who fail initial therapy for mild disease)
  - Oral corticosteroids (to promote disease remission)
  - Immunomodulators (azathioprine, mercaptopurine, methotrexate) to promote or maintain disease remission
  - Anti-TNF antibodies (infliximab, adalimumab…)

- **MODERATE** who fail above therapies or **SEVERE**:
  - IV corticosteroids
  - Anti-TNF antibodies
  - Surgery
  - Natalizumab (ab-alpha 4 integrin) (those who have failed immunomodulators or TNF antagonists)
  - Cyclosporine (those with severe UC who have failed IV corticosteroids)
Therapeutic Pyramid Approach to IBD