Gastrointestinal Pharmacology

Part 1: Peptic Ulcer Disease and Reflux Esophagitis

PEPTIC ULCER

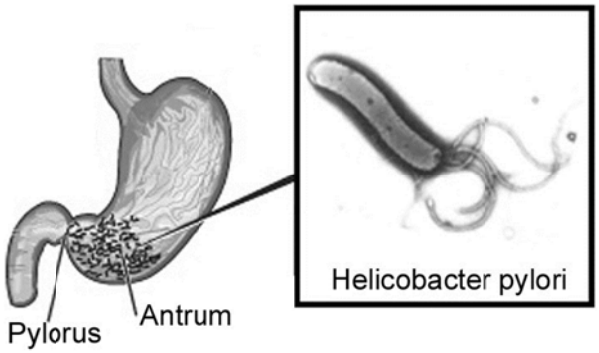
Definition: ulceration of the duodenum or stomach due to imbalance between local invasive force (e.g. HCl and pepsin) and protective mechanisms.

Invasive factors:

- Stress: ↑ HCl and pepsin secretion by parietal cells.
- Diet: coffee, alcohol and spices.
- **Drugs:** NSAIDs, corticosteroids, morphine, methylxanthines, etc.
- **Infection** with ***Helicobacter pylori.***
  H. pylori is spiral gram –ve flagellates found in the antrum of human stomach. Certain enzymes and toxins produced by the bacteria cause tissue damage. Infection with *H. pylori* can be diagnosed by endoscopic biopsy or serological markers.

Defensive mechanisms:

- Mucus production by gastric mucosa.
- Pancreatic bicarbonate secretion.
- Good mucosal blood flow.
- Local PGE_2 and PGI_2 production.

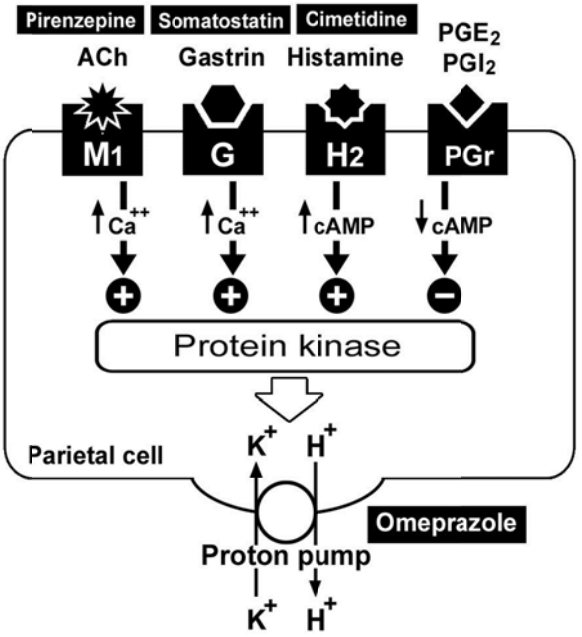


Regulation of HCl secretion

- **Ach:** ↑ HCl secretion through $\mathbf{M_1}$ receptors → ↑ intracellular Ca^{2+}.
- **Gastrin:** ↑ HCl secretion through **G** receptors → ↑ intracellular Ca^{2+}.
- **Histamine:** ↑ HCl secretion through $\mathbf{H_2}$ receptors → ↑ intracellular cAMP.

Both Ca^{2+} and cAMP activate H^+/K^+ *ATPase* at the membrane of the parietal cell to secrete H^+ into the gastric lumen **"proton pump"**.

- **PGE_2** and **PGI_2:** act on PG receptors → ↓ cAMP → ↓ HCl secretion.

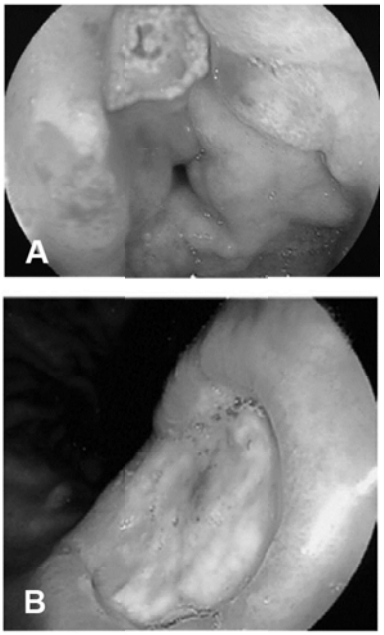


Clinical picture

- Epigastric pain: characterized by:
  - Diffuse and worsens by food in **GU.**
  - Localized (point tenderness) and relieved by food in **DU.**
- Signs of complications e.g. bleeding, anemia, etc.

Diagnosis

- Endoscopy: visualization of the ulcer.
- Radiologic: by barium meal.



Endoscopic views. (a) Duodenal ulcer with inflamed duodenal .folds. (b) Benign gastric ulcer

Therapy of peptic ulcer

Non-drug therapy = life style modification

- Rest and **S**edation: they improve healing and relief pain of DU.
- Stop **S**moking, **S**pices, alcohol, coffee, and tea: because they ↑ HCl.
- Avoid **S**tress: because stress ↑ HCl.
- Avoid ulcerogenic drugs: e.g. NSAIDs.
- Diet:
  - Frequent small meals in DU in order to buffer high acidity.
  - Encourage milk and fats.
  - Avoid **S**pices and fried food

Pharmacological therapy

- **Drugs that neutralize HCl:** antacids
- **Drugs that ↓ HCl secretion:**

- Selective M_1 blockers: pirenzepine, telenzepine.
- H_2 blockers: cimetidine, ranitidine, famotidine.
- Proton pump inhibitors: omeprazole, lanzoprazole, etc.

- **Drugs that ↑ mucosal defense mechanisms:**
  - Sucralfate
  - Colloid bismuth compounds: e.g. bismuth subcitrate.
  - Carbenoxolone
  - PGE_1 analogues: misoprostol.

- **Antimicrobial drugs** for *H. pylori*: see later.

- **Adjuvant therapy:** Sedatives and multivitamins to ↓ stress to enhance healing.

ANTACIDS

- Antacids are weak bases that are taken orally and partially neutralize gastric acid and reduce pepsin activity.
- They are used as **symptomatic relief** of hyperacidity and should **not** be used as long-term treatment.

Sodium bicarbonate	Calcium carbonate	Magnesium and aluminum salts (Mg hydroxide and Aluminium hydroxide)
▪ It can be **absorbed** systemically leading to salt & water retention, and metabolic alkalosis. ▪ It is contraindicated in hypertension and heart failure. ▪ It has **rapid** onset and short duration.	▪ **Partially** absorbed antacid. ▪ Ca^{2+} may act directly to stimulate gastrin secretion leading to acid rebound. ▪ It is contraindicated in hypercalcemia and renal stones.	▪ They are **poorly** absorbed from GIT and have no systemic effects. ▪ The unabsorbed Mg salts cause osmotic **diarrhea**; the unabsorbed Al salts cause **constipation**. ▪ They have **slow** onset.

Adverse effects

- **Change in bowel habits:** Al^{3+} hydroxide causes *constipation*, while Mg^{2+} hydroxide cause *diarrhea*. For this reason, both salts are combined together to manage this problem.

- **Rebound hyperacidity:** with Ca^{2+} and $NaHCO_3$ containing antacids.
- **Cation overload:**
  - Na^+ salts → hypertension and systemic alkalosis.
  - Ca^{2+} salts → hypercalcemia, renal stones and **milk-alkali syndrome.**

Milk-alkali syndrome

Patients with PU usually administer large amounts of milk and antacids to relieve symptoms of hyperacidity.

- Excess milk ⟶ hypercalcemia.
- Excess antacids ⟶ alkalosis (due to continuous wash of HCl).

- **Decrease absorption of other drugs:** the metal ion in some preparations can chelate other drugs especially tetracycline, digitalis and iron.

N.B. when **iron** or **tetracycline** is prescribed with antacids, we should make **30 min** interval between both drugs to avoid **chelation** with the antacid.

DECREASE HCL SECRETION

1. Selective M_1 blockers:

(Pirenzepine - Telenzepine)

Mechanism of action: selectively block gastric M_1 receptors → ↓ **basal** HCl secretion.

Uses: The selective M_1 blockers are **weak** inhibitors of HCl secretion and are now replaced by more effective drugs. They are sometimes used as adjuvant therapy with H_2 blockers.

Adverse effects: high doses produce atropine-like effects: dry mouth, blurred vision, tachycardia, urine retention.

N.B. Atropine itself is not used in the treatment of PU because it is non-selective M blocker and **may aggravate esophageal reflux.**

2. H2 blockers:

(Cimetidine – Ranitidine – Famotidine - Nizatidine)

Mechanism and pharmacological effects

- They act as competitive inhibitors of histamine H2-receptors on the parietal cell. This results in a marked ↓ in histamine-stimulated HCl secretion.
- Although other agents such as gastrin and ACh may induce acid secretion, histamine is the predominant final mediator that stimulates HCl secretion.

Therapeutic uses

- Duodenal and gastric ulcers.
- Prophylaxis & treatment of stress ulcers (e.g. after burn or major trauma).
- Prophylaxis against bleeding of esophageal varices.
- Reflux esophagitis.
- Zollinger-Ellison syndrome (gastrin-secreting tumor of the pancreas which ↑ HCl secretion): usually larger doses are required.
- With ulcerogenic drugs (e.g. NSAIDs) to protect the gastric mucosa from injury.

Adverse effects (mostly with cimetidine):

– **Cimetidine** has **anti-androgenic effects** (due to block of androgen receptors) leading to ↓ sperm count, impotence and gynecomastia.
– **Cimetidine** inhibits **hepatic microsomal enzymes (P450)** leading to ↓ metabolism of other drugs e.g. theophylline, warfarin, sulphonylureas, etc.
– **R**eversible hepatotoxicity and **R**eversible anemia.
– **CNS** symptoms: headache, slurred speech, delirium, coma, etc. occurs mainly in **elderly people** with **i.v.** administration.

Precautions of H2 blockers

– Avoid sudden withdrawal to prevent rebound ulceration.
– Avoid their use in pregnancy and lactation (they cross the placental barrier and secreted in breast milk).
– Avoid combination of cimetidine with drugs having narrow therapeutic index (because cimetidine inhibits microsomal P450 and ↑ their toxicity).

	Cimetidine	Ranitidine	Famotidine
H_2 Blocking effect:	Weak	Potent	More potent
Anti-anderogenic effect:	Strong	Minimal	No
Liver enzyme inhibition	Strong	Minimal	No
Adverse CNS effects:	Frequent	Less frequent	Less frequent
Duration of action:	8 h	12 h	24 h
Dose:	**800** mg/day for 6-8 weeks then **400** mg/day for 6-8 months	**300** mg/day for 6-8 weeks then **150** mg/day for 6-8 months	**20** mg/day for 6-8 weeks then **10** mg/day for 6-8 months

3. Proton pump inhibitors (PPIs):
(Omeprazole – Lansoprazole – Pantoprazole)

Chemistry: all are imidazole derivatives.

> ▶ **Imidazole derivatives:**
> 1. **Nasal decongestants:** Nafazoline
> 2. **Antimicrobials:** Metronidazole
> 3. **Antifungal:** Ketoconazole
> 4. **Antiparasitic:** Mebendazole
> 5. **Proton pump inhibitors:** Omeprazole

Mechanism of action

- They are **prodrugs**. They are converted into the active form in the gastric mucosa and produce **irreversible inhibition** of gastric H^+/K^+ *ATPase* enzyme leading to ↓ both **basal** and **stimulated** HCl secretion to around the **zero** level for 1-2 days.
- Full restoration of acid secretion after stopping the PPI takes about 3-5 days (time of re-synthesis of H^+/K^+ *ATPase*).
- Their bioavailability is decreased significantly by food and, ideally, should be administered 1 hour before a meal.

Therapeutic uses: The same as H_2 blockers **(dose of omeprazole: 20-40** mg/day orally for 4-6 weeks then **10-20** mg/day for 4-6 months to prevent recurrence).

Adverse effects

– Low incidence of diarrhea, abdominal colic, dizziness, skin rash, **leucopenia**, and transient increase of liver enzymes.
– **Decrease vit B_{12} absorption** after > 12 weeks of therapy due to interference with intrinsic factor secretion by the stomach.
– Inhibition of gastric acidity leads to **alteration of bioavialability of some drugs** e.g. ketoconazole, digoxin, and iron.
– Omeprazole **inhibits microsomal P450 enzymes** and decreases metabolism of phenytoin, warfarin, and cyclosporin. Newer PPIs do **not** affect liver enzymes.
– Omeprazole in high dose induced gastric **carcinoid tumor** in rats.

ENHANCING MUCOSAL DEFENSE MECHANISMS

1. Sucralfate

- It is an aluminum salt of sulfated sucrose.
- Slightly (3%) absorbed from the GIT. The aluminum metal may accumulate in cases of renal failure, so it should be avoided in **renal failure**.

Mechanism of action

- It **needs acidic medium** to be activated. In the presence of acidic medium, it

forms a complex with protein debris at the ulcer base and forms a physical barrier (so **not** taken with antacids, H_2 blockers, or PPIs).
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

– Constipation (due to presence of aluminum).
– ↓↓ absorption of tetracycline, digoxin and phenytoin.

N.B. Both sucralfate and bismuth compound are **not given** simultaneously with antacids or H_2 blockers (at least **30** min must be elapsed in-between). **Why?**

2. Bismuth compounds:
Bismuth subsalicylate and subcitrate

Mechanism of action

- In acidic pH, it forms a complex with protein debris at the ulcer base and forms a physical barrier.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.
- It has **additional antimicrobial activity** against *H. pylori.*

Adverse effects

– Stool and teeth discoloration.
– **Encephalopathy** in presence of **renal failure**

Contraindications: Chronic renal failure and CNS diseases.

3. Carbenoxolone

It is a *liquorice* derivative having **steroid** structure.

Mechanism of action

- It ↑ production and viscosity of gastric mucus and ↑ mucosal resistance.
- It ↓ pepsin secretion and ↑ secretion of endogenous PGs.

Adverse effects

Salt & water retention (aldosterone-like effects) → edema and hypertension especially in cardiac and renal patients. This edema can be treated by thiazide diuretics (**not by spironolactone)** because both spironolactone and carbenoxolone have steroid structure and can compete with each other.

Contraindications: Hypertension and/or renal failure

4. Synthetic PGE1 analogue: Misoprostol

Mechanism of action

- It acts on specific receptors on gastric parietal cells to ↓ histamine-stimulated HCl secretion.
- ↑ mucus and bicarbonate secretion (cytoprotective action).
- ↑ mucosal blood flow and stimulates mucosal cellular regeneration.

Therapeutic uses

Prevention of peptic ulcer in high risk patients e.g. those on long term use of NSAIDs for chronic inflammatory diseases. [**misoprostol** 200 μg is combined with **naproxen** or **diclofenac** in single tablet].

Adverse effects

– Diarrhea and cramping pain: due to ↑ GIT motility and water secretion.
– Uterine contractions during pregnancy → **abortion.**

Contraindications: pregnancy.

ERADICATION THERAPY FOR *H. pylori*

- Infection with *H. pylori* is a **main cause of recurrence** of PU.
- The following 10 days ***"sequential protocol"*** is highly effective for eradication of *H. pylori*:

PPIs
Amoxicillin 1 g
twice daily for 5 days (days 1-5).

PPIs
Clarithromycin 500 mg
Tinidazole 500 mg
twice daily for 5 days (days 6-10).

THERAPY OF BLEEDING PEPTIC ULCER

- **Hospitalization** and **Fresh blood transfusion**.
- **Acid suppression with high dose PPIs** by continuous i.v. infusion is the standard of care e.g. omeprazole 80 mg i.v. bolus followed by 8 mg/h for 72h.
- **Vitamin K_1:** 10 mg i.m or s.c.
- **Endoscopic therapy:** several types of endoscopic treatments are available.

TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Definition: reflux of gastric contents into the esophagus due to incompetent lower esophageal sphincter (LES). **Heartburn** and chest pain are the major complain which may be misdiagnosed of angina pectoris.

Non-drug therapy = life style modification

- **Head of bed elevation:** because most damage to the esophagus occurs at night when HCl can remain in contact with the mucosa for long period.
- **Weight reduction.**
- **Avoid:**
  - **S**tress, **S**moking, **S**pices, alcohol.
  - Ulcerogenic **drugs** e.g. NSAIDs.

Drugs ↑ LES pressure:

- Metoclopramide
- Domperidone
- Bethanechol
- Erythromycin

Drugs ↓ LES pressure:

- Anticholinergic drugs
- Nitrates

Drug therapy

- Decreasing HCl secretion: H_2 blockers and proton pump inhibitors.
- Prokinetic drugs.
- Antacids and antacid combinations: (Gaviscon).

Surgical treatment: if medical therapy failed.

PROKINETIC DRUGS

Definition: they are drugs that increase **upper GIT motility** and enhance gastric emptying. They include:

- **Dopamine antagonists:** e.g. Metoclopramide and Domperidone.
- **Serotonin (5-HT4)** agonists: e.g. Mosapride
- **Cholinomimetic agents:** e.g. Bethanechol.
- **Macrolide antibiotics:** e.g. Erythromycin

1. Metoclopramide

Mechanism and pharmacological effects

- Metoclopramide ↑ LES tone and enhances gastric emptying and **upper** GIT motility through:
  - Blocking of dopamine (D) receptors (central & peripheral) leading to decrease the inhibitory action of dopamine on the GIT motility.
  - Enhances cholinergic transmission in the upper GIT.

- **N.B.** Metoclopramide has **no effect** on small intestinal or colonic motility.

- **Antiemetic action:** due to blockade of D2 receptors in the chemoreceptor trigger zone of the medulla (**CTZ).**

Therapeutic uses

- **Gastroesophageal reflux:** to enhance gastric emptying and ↑ LES pressure.
- **Disorders of gastric emptying**: e.g. diabetic gastroparesis and postoperative gastric retention.
- **Before small bowel endoscopy** (20 mg given by slow i.v.i.): to enhance gastric evacuation and peristaltic movement. Also to prevent vomiting.
- **Before emergency surgery** and labor to evacuate the stomach and prevent aspiration of gastric contents during anesthesia.
- **Treatment of nausea and vomiting** of various causes.

Adverse effects

- Sedation (the most common adverse effect).
- **Extrapyramidal effects** (e.g. *dystonia* and *dyskinesia*): (especially in **old age**) due to blockade of D_2 in the *basal ganglia*.
- **Hyperprolactinemia** due to blockade of D_2 in the *pituitary gland*.

Drug interactions

- **Anticholinergic drugs (e.g. atropine)** antagonize its prokinetic action.
- **Other dopamine blockers** (e.g. antipsychotic drugs) administered with metoclopramide may precipitate acute extrapyramidal effects.

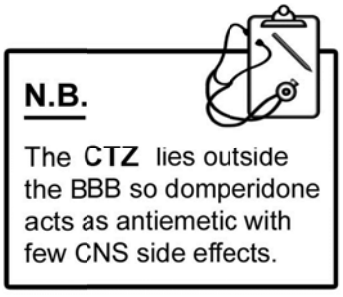
2. Domperidone

Mechanism and pharmacological effects

- **It blocks peripheral D_2 receptors leading to** ↓ the inhibitory action of dopamine on GIT motility. It does **NOT** cross BBB so it has no CNS side effects.
- **Antiemetic effect** less than metoclopramide.

Therapeutic uses

- The same uses as metoclopramide.
- To counteract nausea and vomiting caused by **levodopa** and **bromocriptine** during treatment of **Parkinson's disease** because it blocks D2 receptors in the CTZ responsible for vomiting but does **not** block D2 receptors in the basal ganglia responsible for parkinsonism.



Adverse effects: there is growing evidence that domperidone may ↑ QT interval and predispose to serious arrhythmia and sudden death.

	Metoclopramide	Domperidone
Dopamine receptor blockade	Central and peripheral	Peripheral only
Cholinergic transmission	Increase	No effect
Antiemetic effect	Strong	Weaker
Extra-pyramidal side effects	Present	No
Hyperprolactinemia	Significant	Minimal

3. Bethanechol

Bethanechol stimulates muscarinic M3 in the smooth ms of the GIT and myenteric plexus. It was used in the past for the treatment of GERD and gastroparesis, but now, it is rarely used for this indication due to multiple cholinergic side effects.

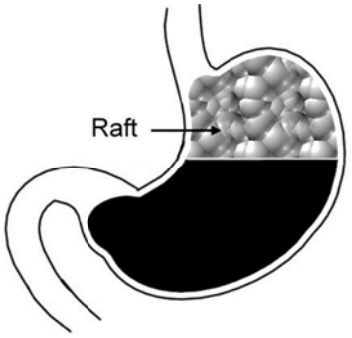
4. Macrolide antibiotics: erythromycin

Macrolide antibiotics such as erythromycin directly stimulate **motilin receptors** on GIT smooth muscle and promote the onset of a migrating motor complex. Intravenous erythromycin (3 mg/kg) is beneficial in some patients with gastroparesis; however, tolerance rapidly develops. It may be used in patients with acute upper GIT hemorrhage to promote gastric emptying of blood before endoscopy.

ANTACIDS AND ANTACID-ALGINIC ACID PRODUCTS

Gaviscon: (alginic acid + Mg-trisilicate + Al-hydroxide + $NaHCO_3$):

Alginic acid in presence of saliva and $NaHCO_3$ forms a highly viscous foamy solution of Na-alginate that floats on the gastric contents as a **raft** and prevents gastric reflux.



H2 BLOCKERS AND PPIS

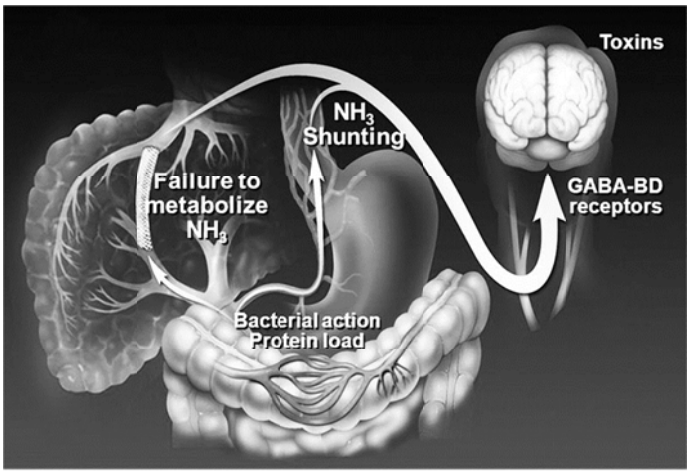
- PPIs are **more effective** than H2 blockers for the treatment of GERD.
- Once-daily dosing of PPIs provides effective symptom relief and tissue healing in 85–90% of patients; up to 15% of patients require twice-daily dosing.

Part 2: Management of Liver Disease Complications

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Definition and pathogenesis

Hepatic encephalopathy is the syndrome of disordered consciousness and neuromuscular activity seen in patients with acute or chronic liver failure.



Pathogenesis of portosystemic encephalopathy

The failing liver cannot metabolize **ammonia** and **benzodiazepines-like mediators (GABA-like transmitters)** generated by the intestinal bacteria. These toxins are shunted directly to the CNS causing encephalopathy.

Management: Treatment is aimed at **reduction of hyperammonemia:**

- **Diet:**
  - **Protein restriction** to decrease formation of ammonia by intestinal bacteria.
  - **Vegetable** protein is better tolerated than animal protein.
  - The rationale and benefit of dietary protein restriction is **controversial**.

- **Enemas**: cleansing of the colon is a rapid and effective method to remove ammoniagenic substrates. It can be done with lactulose or tape water.

- **Lactulose:**
  - It is synthetic non-absorbable disaccharide. In the colon, it is transformed by bacteria into **lactic** and **acetic** acids → ↓ pH of the colonic medium **leading to:**
    - Inhibition of intestinal bacteria → ↓ production of ammonia.
    - ↑ transport of ammonia from blood to intestinal lumen where it is converted to the poorly absorbed ammonium ion.
    - Osmotic laxation → ↑ excretion of ammonium ion.
  - It is administered orally or as enema (for patients in coma).
  - **Adverse effects:** relatively safe drug.

- **Oral antibiotics:**

  Neomycin:
  - It is non-absorbable aminoglycoside antibiotic.

– It ↓ blood ammonia by killing intestinal bacteria that generate ammonia.
– It is used in a dose of 1-2 g 4 times daily orally or as retention enema.
– Small amounts of neomycin may be absorbed (~1%) and result in ototoxicity and nephrotoxicity especially in patients with renal impairment.

Other antibiotics:

– **Metronidazole** acts on anaerobic bacteria. It is the preferred option if there is fear from adverse effects of neomycin (but given for short term).
– **Rifaximin:** is non-absorbable and better tolerated antibiotic.

MANAGEMENT OF VARICEAL BLEEDING DUE TO PORTAL HYPERTENSION

Management of acute bleeding

- **Fresh blood transfusion.**
- **Acid suppression** with **omeprazole** (80 mg) to minimize HCl irritation.
- **i.v. vasopressin or its analogues:**
  - **Vasopressin:**
  – It produces mesenteric VC leading to ↓ portal venous flow and pressure.
  – It can produce systemic VC (coronary, cerebral, limb, etc), so it is better combined with i.v. **nitroglycerine** to reduce systemic and coronary VC.
  – The vasopressin/nitroglycerine combination is **rarely** used now.
  - **Terlipressin:**
  – It is synthetic analog of vasopressin that is released in a slow and sustained manner allowing more sustained hemodynamic effects with fewer systemic side effects than vasopressin.
- **Prophylactic antibiotics:** to prevent infectious complications after GI hemorrhage. The preferred antibiotic is **i.v. ceftriaxone** 1 gm/day for 7 days.
- **Endoscopic sclerotherapy:** injection of the varices with a sclerosing agent to induce fibrosis and obliteration.

Prevention of re-bleeding (prophylaxis):

- **Beta-blockers (propranolol** 40 mg twice daily). It ↓ portal BP through:
  – They ↓ COP → ↓ portal blood flow.
  – They cause unopposed α- action → VC of the splanchnic vascular bed.
- **H_2 blockers or PPIs:** to prevent gastroduodenal erosions.
- **Metoclopramide:** to enhance gastric evacuation and ↑ LES pressure.

Part 3: Antiemetic Drugs

Several classes of antiemetic drugs are available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting. The antiemetic drugs are classified according to their primary action; some agents affect multiple receptors.

Drug	Antiemetic mechanism	Uses as antiemetic	Adverse effects
1. Muscarinic blockers: ▪ Atropine ▪ Hyoscine	They block **M_1** receptors in the vestibulocerebellar pathway, solitary tract nucleus, and chemoreceptor trigger zone (CTZ).	Prevention and treatment of vomiting due to **motion sickness** (0.3-0.6 mg/8 hrs orally).	– Blurred vision – Dry mouth – Urine retention – Glaucoma – Tachycardia
2. H1-blockers: ▪ Diphenhydramine ▪ Cyproheptadine ▪ Cyclizine ▪ Meclizine	– They block H_1 (also M_1) receptors in the vestibulo-cerebellar pathway and CTZ. – They have sedative action.	– Vomiting due to **motion sickness** (diphenhydramine) – Vomiting of **pregnancy** (cyclizine and meclizine) – **True vertigo**: combined with VDs to improve labyrinthine blood flow.	– Sedation (excitation may occur in children). – Atropine-like actions (dry mouth, blurred vision, urine retention). – Hypotension
3. 5-HT3 blockers: ▪ Ondansetron ▪ Granisetron ▪ Tropisetron	They block $5HT_3$ receptors in the GIT, solitary tract nucleus and CTZ.	– Vomiting due to **cancer chemotherapy** or **radio-therapy.** – **Postoperative** nausea and vomiting.	– Dizziness, headache, and constipation.
4. Dopamine blockers ▪ Metoclopramide	– They block D2 receptors in the CTZ.	– Vomiting due to **drugs** or fevers.	– Sedation – Extrapyramidal effects e.g.

▪ Domperidone ▪ Phenothiazines e.g. chlorpromazine	– They inhibit peripheral transmission to VC.	– Vomiting due to **cancer chemotherapy**. – **Postoperative** nausea and vomiting.	dystonia and dyskinesia. – Hyperprolactinemia – Postural hypotension
5. Cannabinoid derivatives: ▪ Nabilone and Dronabinol	– It is a partial agonist at central and peripheral cannabinoid receptors (CB1). The exact mechanism is unclear.	– Vomiting due to **cancer chemotherapy** – Patients refractory to other antiemetics.	– Sedation – Hallucinations – Psychotropic effects – Postural hypotension – Drug abuse.
6. Vitamin B6 (pyridoxin)	May be related to the balance between GABA (CNS *inhibitory* transmitter) and glutamate (CNS *excitatory* transmitter).	– Vomiting in **pregnancy** (50 mg at bedtime). – Vomiting in **children**	-
7. Corticosteroids ▪ Dexamethasone ▪ Prednisolone	The exact mechanism is unclear.	– Combined with Vit B6 to treat vomiting in **pregnancy**. – Vomiting due to **cancer chemotherapy**.	– See endocrine chapter
8. Benzodiazepines ▪ Lorazepam ▪ Diazepam	Allosteric facilitation of central GABA inhibitory transmission	– **Stress-related** vomiting – To controls symptoms in **Ménière disease**	– See CNS chapter
9. Neurokinin-1 receptor blockers: ▪ Aprepitant	Substance-P induces vomiting through stimulation of NK-1 receptors. Aprepitant blocks this receptor.	– In combination with 5-HT3 blockers to treat vomiting due to **cancer chemotherapy**	– Diarrhea and fatigue

Part 4: Antispasmodic Drugs (smooth ms relaxants)

Classification

- **Anticholinergic drugs:** atropine, hyoscine, propantheline, oxyphenonium.
- **Direct smooth muscle relaxants:** papaverine, mebeverine, alverine, drotaverine.
- **Mixtures:** Librax (clidinium + chlordiazepoxide), Donnatal (hyoscine + phenobarbital).

<table>
<tr><th></th><th>Papaverine</th><th>Mebeverine, Alverine, Drotaverine</th><th>Librax</th></tr>
<tr><td rowspan="2">Chemistry & mech-anism of action</td><td>It is opium alkaloid but chemically different from morphine</td><td>They are synthetic drugs</td><td rowspan="2">It is a combination of:
▪ Chlordiazepoxide: benzodiazepine that has antianxiety effect.
▪ Clidinium: anticho-linergic drug which ↓ GIT motility and spasm</td></tr>
<tr><td colspan="2">The exact mechanism is unclear but may be due to inhibition of PDE enzyme →↑ cAMP → smooth muscle relaxation.</td></tr>
<tr><td>Use</td><td colspan="3">▪ Spasms of the GIT, bile duct and genitourinary tract.
▪ Librax is used for treatment of irritable bowel syndrome (IBS).</td></tr>
<tr><td>Side effects</td><td colspan="2">– Cardiac arrhythmia.
– Abnormal liver functions in the form of elevated serum transaminases and alkaline phosphatase.
– Headache and dizziness</td><td>– Atropine-like actions e.g, dry mouth, urine retention, etc.
– Sedation, drowsiness, confusion, etc.</td></tr>
<tr><td>C/I</td><td colspan="3">– Paralytic ileus.
– Constipation for more than one week</td></tr>
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Part 5: Therapy of Constipation

Non-drug therapy: It is the **first line** in all cases of constipation

- **Diet rich in fibers** e.g. fruits, vegetables, whole meal bread, etc. to be increased to 30 g/day.
- Increase **fluid intake**
- Minimize **tea** and coffee.
- Physical **exercise** to activate abdominal muscles and intestinal peristalsis. This help food move more efficiently through the gut.

Drug therapy: LAXATIVES:

Drug causes of constipation:

- **A**tropine and related drugs.
- **Al**uminum containing antacids
- **A**dsorbents (kaolin & pectin).
- **CCBs:** e.g. **V**erapamil
- **Opioids:** morphine & loperamide

1. Bulk-forming agents:

[Dietary fibers – Methylcellulose – Bran]

Mechanism of action

They are non-digestible fibers; they retain water in the gut and distend the large intestine → activation of stretch receptors → stimulation of peristalsis.

Adverse effects: they are **safe** laxatives but may cause:

- Bloating and abdominal distension.
- ↓ absorption of some drugs e.g. digoxin.
- They may form masses in the gut leading to intestinal obstruction.

2. Osmotic laxatives:

[Mg sulfate & Na salts – Lactulose – Polyethylene glycol]

Mechanism of action

They are retained in the gut lumen and retain water by their osmotic effect → activation of stretch receptors → stimulation of peristalsis.

Adverse effects

- Mg & Na salts (saline laxatives) may be absorbed systemically and produce *hypermagnesemia* and *hypernatremia* especially in patients with renal failure.
- Lactulose may produce abdominal discomfort.
- Polyethylene glycol may produce electrolyte disturbance (hypokalemia).

3. Irritant (or stimulant) laxatives:

[Castor oil – Senna – Bisacodyl]

Mechanism of action

They produce inflammation (irritation) of the intestinal mucosa and inhibit Na^+/K^+ *ATPase enzyme* leading to:

- Accumulation of water and electrolytes in the gut lumen.
- Direct stimulation of peristalsis by their irritant effect.

Adverse effects

Castor oil
- Bad taste.
- Stimulation of uterine contraction and **abortion**

Senna
- It passes in urine and cause **urine discoloration**
- It passes in breast milk and cause **cathartic** effect in the baby.
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon.
- Increase menstrual blood flow and **abortion** in pregnancy.
- **Laxative dependence:** Irritant laxatives cause complete evacuation of the colon. The colon requires 2-5 days before the normal fecal mass can be reestablished. The patient becomes worry regarding the lack of bowel movement during this period and may use the laxative again and a vicious cycle is established leading to partial or complete loss of normal bowel function.

Bisacodyl
- It is prepared as enteric coated tablets to avoid gastric irritation. If it is given with milk or with other drugs that change gastric pH, the enteric coating may dissolve in the stomach and cause gastric irritation and pain
- Prolonged use → degeneration of gut nervous plexus → **atonic** (cathartic) colon *(should not be used more than 10 days).*

4. Stool softeners: Docusate sodium

Mechanism: they are anionic surfactants that enable additional water and fats to be incorporated in the stool, making it easier to move through the GIT.

5. Lubricant laxatives:

[Liquid paraffin – Glycerin suppositories – Evacuant enema]

Mechanism of action

- **Paraffin oil** it coats the fecal matter and retards water absorption by the colon.
- **Glycerin** has hygroscopic effect. It draws water from rectal mucosa and lubricates the anal canal. It also stimulates reflex rectal contractions and promotes stool evacuation in 15-20 min.

N.B.
►Evacuant enemas:
- Solutions (small volume) of tape water (135 ml) with added mineral oil, hypertonic sorbitol, MgSO4, docusate K.
- All are safe for self-administration to facilitate passage of stool in painful conditions of the anus.

Adverse effects: paraffin oil decreases absorption of fat-soluble vitamins

6. Chloride channel activators: Lubiprostone

Mechanism of action

It acts by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stool and causes little change in electrolyte balance.

General indications of laxatives

- **Constipation:** laxatives should not be used for prolonged duration to avoid laxative dependence.
- To fasten excretion of **toxic** substances from the GIT.
- To prepare the bowel before **X-ray** or colonoscopy.
- Hepatic encephalopathy (lactulose): to kill ammonia producing bacteria.
- Painful anal conditions e.g. anal fissure or piles.
- Postoperative: e.g. after hemorrhoids (piles) to avoid strain.

Contraindications of laxatives

- Laxatives are dangerous in cases of undiagnosed abdominal pain or inflammatory bowel disease. They may lead to intestinal perforation.
- Organic obstruction of the GIT.

Part 6: Therapy of Diarrhea

Causes of diarrhea

- **Infectious diarrhea:** bacterial, viral, fungal, protozoal, etc. Infectious diarrhea is the most common type.
- **Hormonal (secretory) diarrhea:** e.g. *serotonin* in carcinoid syndrome; *calcitonin* in medullary thyroid carcinoma, *histamine* in mastocytosis, *thyroxine* in hyperthyroidism. Diarrhea is caused by: (1) increased water secretions into the intestinal lumen and (2) increased intestinal motility.
- **Malabsorption syndromes:** e.g. bile acid malabsorption
- **Inflammatory (exudative) diarrhea:** caused by inflammatory bowel diseases e.g. *Crohn's disease* (transmural lesion in the small intestine) and *ulcerative colitis* (ulceration of the colon with bloody diarrhea).
- **Iatrogenic (drug induced) diarrhea:**
  - Overuse of laxatives.
  - Mg-containing antacids.

- Antibiotic-associated diarrhea (*pseudomembranous colitis*) see chemotherapy
- Cholinomimetic drugs.

Patterns of diarrhea

- **Acute self-limited diarrhea:** acute diarrhea disappears within 24 hrs.
- **Acute diarrhea (<2 weeks):** passage of watery stool more than 10 times/day associated with dehydration and electrolyte imbalance.
- **Chronic diarrhea: (>2 weeks):** persistent diarrhea for **3** weeks in adults or **4** weeks in infants. It causes weight loss and weakness.

Investigations of diarrhea

- **Stool examination:**
  - Macroscopic: consistency, color, blood, etc.
  - Microscopic: RBCs, WBCs, parasites, ova, etc.
  - Stool culture and sensitivity tests.
- **Endoscopy** and biopsy in chronic cases.
- **Radiologic** examination: by barium enema.

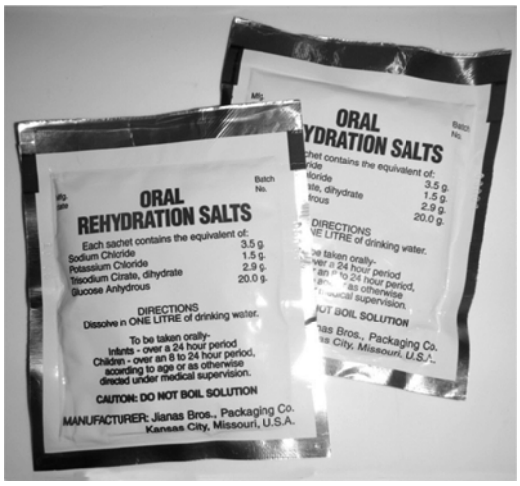
Treatment of diarrhea

Lines of therapy

- **Maintenance of fluid and electrolyte balance:** is the **first** priority.
- **Non-specific antidiarrheal agents:** should be applied after exclusion of other relevant causes of diarrhea.
- **Specific antidiarrheal agents:** treatment of the cause e.g.
  - Antimicrobials for infectious diarrhea.
  - Antiinflammatory drugs for inflammatory bowel diseases.
- **Antispasmodic drugs:** if there is colic or abdominal cramps.

I. MAINTENANCE OF FLUID AND ELECTROLYTE BALANCE

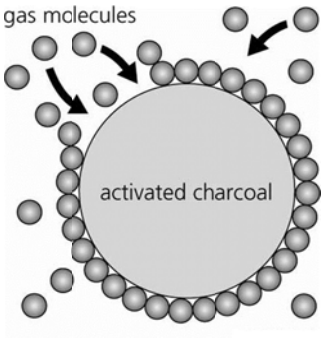
- **Oral Rehydration Therapy (ORT):**
  - Balanced salt solution containing electrolytes and glucose (glucose is important for sodium and consequently water absorption).
  - 90% of acute cases of childhood diarrhea can be corrected using ORT only.
- **Intravenous solutions:** if dehydration is severe.



N.B. in infants with dehydration, **blood pH, serum Na^+ and K^+** must be measured before giving any **i.v. solution** to avoid electrolyte and acid/base imbalance.

II. NON-SPECIFIC ANTIDIARRHEAL THERAPY

1. Adsorbents: Kaolin, pectin, activated charcoal



Mechanism

- They adsorb water, microoganisms and toxins.
- They coat the mucosa and protect it.

Adverse effects: they may ↓ absorption of other drugs.

2. Bismuth subsalicylate

Mechanism

- Bismuth: provides a **protective coat** for the mucosa and **binds toxins** produced by pathogenic bacteria.
- Subsalicylate: hydrolyzed by intestinal bacteria into **salicylic acid** →↓ intestinal inflammation, hypermotility and secretions.

3. Anti-cholinergic drugs: atropine, hyoscine and propantheline

Mechanism

- Antidiarrheal action: ↓ colonic peristalsis by blocking the response of intestinal smooth muscle to cholinergic stimulation.
- Antispasmodic action: relieve cramps associated with diarrhea.

4. Synthetic opioid preparations: diphenoxylate and loperamide

Mechanism

- They act on opioid **μ (mu)** and **δ (delta) receptors** in the enteric nervous system (both pre- and postsynaptic) leading to:
  - ↑ segmenting (non-propulsive) contractions of the small intestine.
  - ↑ water absorption and ↓ water secretion by intestinal mucosal cells.
  - ↓ Ach release by cholinergic neurons in the ENS.
- Loperamide **cannot cross BBB** while diphenoxylate can **cross BBB in very small amount** (no CNS effects in **usual** therapeutic doses) but it can cause addiction if used in large doses and for prolonged duration.
- They are commonly **combined with atropine** (e.g. **Lomotil®** is a combination of

diphenoxylate 2.5 mg + atropine 0.25 mg) to produce more ↓↓ in intestinal motility and decrease liability for abuse.

Adverse effects

- Anti-cholinergic side effects e.g. dry mouth.
- Addiction: if used for prolonged duration.
- Precipitation of **toxic megacolon** if used in ulcerative colitis.

5. Cholestyramine

Mechanism: it binds **bile acids** in the intestine preventing their absorption and decreasing their irritation.

Therapeutic uses: diarrhea due to **bile salt malabsorption.**

III. SPECIFIC ANTI-INFECTIVE AGENTS

- It is not necessary in simple gastroenteritis as most cases are viral in origin.
- Chemotherapy is necessary in specific types of enteritis e.g.

C. difficile colitis *Clostridium difficile*	**Metronidazole** 400 mg/8h orally for 10 days (1st choice). ***If no response to metronidazole:*** **vancomycin** 250 mg/6h**.**
Campylobacter jejuni	**Azithromycin** 500 mg/day orally for 3 days.
E. coli (enterotoxigenic and enteropathogenic)	**Ciprofloxacin** 500 mg/12h for 1-3 days
Non-typhoid Salmonella spp.	**Ciprofloxacin** 500 mg/12h for 5-7 days or **ceftriaxone** 1g IV/24h.
Shigella spp.	**Ciprofloxacin** 500 mg/12h for 3-5 days or **co-trimoxazole** 2 tab (80/400)/12h.
V. cholerae	**Doxycycline** 300 mg orally single dose or **ciprofloxacin** 500 mg/12h orally for 3 days.
V. parahemolyticus	**Ciprofloxacin** 500 mg/12h for 1-3 days

IV. ANTI-INFLAMMATORY DRUGS

1. Sulfasalazine (5-aminosalicylic acid "5-ASA" + sulfapyridine)

Mechanism: In the colon, the "azo" bond is broken by intestinal bacteria to release 5-ASA and sulfapyridine: 5-ASA has anti-inflammatory and immunosuppressive, while sulfapyridine is poorly absorbed sulfonamide with antibacterial action.

Therapeutic uses:

– Active ulcerative colitis (3-4 gm/day) and to maintain remission (2 gm/day).
– Rheumatoid arthritis.

Adverse effects: mainly due to sulfapyridine (sulfonamide) → drug allergy, bone marrow depression and **megaloblastic anemia** (avoided by giving **folic acid**).

Other aminosalicylates:

- **Mesalazine:** modified-release preparation.
- **Olsalazine** is a dimmer of 5-ASA. It is cleaved in the lower bowel to release 5-ASA.

2. Corticosteroids

Mechanism

– Stimulation of Na^+ absorption from the intestine.
– Anti-inflammatory action (see endocrine).

Therapeutic uses: they are given orally or as enema in severe cases.

– To control acute episodes of Inflammatory bowel diseases
– Refractory diarrhea unresponsive to other agents.

Travellers' diarrhea:

Diarrhea that occurs to travellers and tourists in high endemic areas. Transmission of infection is done through contaminated food or water.

Drug therapy:

– Prophylaxis: doxycycline (100 mg /day orally)
– Treatment: doxycycline + bismuth subsalicylate + fluids

3. Immunosuppressive agents

- **Cytotoxic drugs (azathioprine** and **6-mercaptopurine):** can be used in ulcerative colitis and Crohn's disease in small dose to avoid bone marrow depression.
- **Cyclosporine-A** use is limited for severe cases due to potential toxicity.

N.B.

- **Metronidazol** may be used in **Crohn's disease** to eradicate anaerobic bacteria.
- **Infliximab** (monoclonal antibodies): can be used in **Crohn's disease** to ↓ TNFα.
- **Aspirin** and **indomethacin** may of value in **acute diarrhea** because they ↓ PGs synthesis → ↑ absorption and ↓ secretions of intestinal fluids.
- **Clonidine** (α_2 stimulant) can be used in **diabetic diarrhea** to ↑ intestinal water absorption and ↓ electrolyte secretion.

Part 7: Drug Therapy of Gallstones (cholelithiasis)

Choleretics: are agents that increase bile production e.g. bile acids and bile salts.

Hydrocholeretics: are agents that increase volume of bile e.g. dehydrocholic acid.

Cholagogues: are agents that stimulate the evacuation of gall bladder e.g. olive oil.

The following drugs are used to dissolve non-calcified cholesterol stones:

Chenodeoxycholic acid (CDCA): It ↓ hepatic cholesterol synthesis and ↑ bile acid and phospholipid synthesis.

Ursodeoxycholic acid (UDCA)

- It is a metabolite of chemodeoxycholic acid.
- It is more potent in reduction of hepatic cholesterol synthesis without affecting the endogenous bile acid synthesis.
- Both CDCA and UDCA are given orally in a dose of 10-15 mg/kg/day for 6-12 month.
- Diarrhea is common side effect with CDCA but is unusual with UDCA.

Notes

Review Questions

1. Classify laxatives. Mention the mechanism of action of each class.
2. Mention the mechanism of action and adverse effects of each of the following:
   - Metoclopramide.
   - Cimetidine
   - Omeprazole
   - Senna
   - Lomotil
3. Mention the mechanism of action and therapeutic uses of:
   - Papaverine
   - Sulfasalazine
   - Terlipressin
4. Mention the drug-drug interactions of metoclopramide.
5. Mention 2 drugs used for the treatment of nausea and vomiting due to the following conditions. For each drug, mention the mechanism of action and the main adverse effects:
   - Vomiting due to cancer chemotherapy
   - Motion sickness
6. Give the reason for:
   - Atropine is combined with diphenoxylate in Lomotil preparation.
   - Domperidone, and not metoclopramide, is used for treatment of vomiting due to levodopa.
   - Irritant laxatives should not be given for long period.
   - Folic acid should be supplemented with sulfasalazine during treatment of ulcerative colitis and rheumatoid arthritis.
7. Mention 3 differences between:
   - Metoclopramide and domperidone.
   - Cimetidine and omeprazole.
8. Mention the mechanism and management of portosystemic encephalopathy.
9. Mention the essential lines of the treatment of bleeding esophageal varices.

Of each of the following questions, select ONE BEST answer:

1. Toxicities of cimetidine include which one of the following?
A. Blurred vision
B. Diarrhea
C. Orthostatic hypotension
D. P450 inhibition
E. Sleepiness

2. Which of the following will result from blockade of H2 receptors?
A. Decreased cAMP in cardiac muscle
B. Increased cAMP in cardiac muscle
C. Decreased IP3 in gastric mucosa
D. Increased IP3 in gastric mucosa
E. Increased IP3 in smooth muscle

3. Which of the following is most effective in the treatment of peptic ulcer disease?
A. Cimetidine
B. Lanzoprazole
C. Pirenzepine
D. Ondansetron
E. LSD

4. A 55-year-old woman with insulin dependent diabetes of 40 years' duration complains of severe bloating and abdominal distress, especially after meals. Evaluation is consistent with diabetic gastroparesis. The drug you would be most likely to recommend is:
A. Docusate
B. Dopamine
C. Loperamide
D. Metoclopramide
E. Sucralfate

5. The steatorrhea of pancreatic insufficiency can best be treated by:
A. Cimetidine
B. Misoprostol.
C. Bile salts.
D. Pancreatic lipase.
E. Secretin

6. A drug of choice in the therapy of inflammatory bowel disease is:
A. Sulfadiazine.
B. Sulfasalazine.
C. Sulfapyridine.
D. Sulfamethoxazole.
E. Salicylate sodium

7. An important drug in the therapy of portal systemic encephalopathy is:
A. Lactulose.
B. Lactate.
C. Loperamide.
D. Lorazepam.
E. Doxapine.

8. Bismuth salts are thought to be effective in peptic ulcer disease because they have bactericidal properties against:
A. Escherichia coli.
B. Bacteroides fragilis.
C. Clostridium difficile.
D. Helicobacter pylori.
E. Staphylococcus aureus.

9. Misoprostol has a cytoprotective action on the gastrointestinal mucosa because it:
A. Enhances secretion of mucus and bicarbonate ion.
B. Neutralizes acid secretion.
C. Antagonizes nonsteroidal anti-inflammatory drugs (NSAIDs)
D. Relieves ulcer symptoms.
E. Coats the mucosa.

10. The primary pharmacologic action of omeprazole is the reduction of:
A. Volume of gastric juice.
B. Gastric motility.
C. Secretion of pepsin.
D. Secretion of gastric acid.
E. Secretion of intrinsic factor.

11. Cimetidine slows the metabolism of many drugs because it inhibits the activity of:
A. Monoamine oxidase (MAO)
B. Tyrosine kinase.
C. Hydrogen - potassium - adenosine triphosphatase (H+, K+, ATPase).
D. Phase II glucuronidation reactions
E. Cytochrome P450.

12. The absorption of iron is reduced when large and prolonged doses of which of the following drugs are given?
A. Vitamin C
B. Alum hydroxide.
C. Aspirin.
D. Cimetidine.
E. Lactuolse.

13. Omeprazole, an agent for the promotion of healing of peptic ulcers, has a mechanism of action that is based on:
A. Prostaglandins.
B. Gastric secretion.
C. Pepsin secretion.
D. H+, K+, ATPase.
E. Anticholinergic.

14. An effective antidiarrheal agent that inhibits peristaltic movement is:
A. Clonidine.
B. Bismuth subsalicylate.
C. Oral electrolyte Solution.
D. Pectin.
E. Diphenoxylate.

15. The approved indication for misoprostol:
A. Reflux esophagitis.
B. Regional ileitis.
C. Ulcerative colitis.
D. Prevention of gastric ulceration in patients using large doses of aspirin like drugs.
E. Pathologic hypersecretory conditions such as Zolinger- Ellison syndrome.

16. Metoclopramide has antiemetic properties because it:
A. Lowers esophageal sphincter pressure.
B. Is a central dopamine- receptor antagonist.
C. Is a central opioid receptor agonist
D. Has cholinomimetic properties.
E. Has sedative properties.

17. Fomatidine has the following properties:
A. A potent proton pump inhibitor.
B. A potent antiemetic agent.
C. A potent inhibitory effect on cyt P450.
D. A potent anti-anderogenic action.
E. None of the above.

18. Radiation-induced vomiting can be treated by drugs that act on:
A. 5-HT3 receptors.
B. M1 receptors.
C. H1 receptors.
D. Alpha receptors
E. Beta receptors.

19. Cholesterol gallstones may be dissolved by oral treatment with:
A. Lovastatin.
B. Dehydrocholic acid.
C. Methyl teriary butyl ether.
D. Chenodeoxycholic acid.
E. Monoctanoin.

20. A patient who must take verapamil for hypertension and angina has become constipated. Which of the following drugs would be most suitable as a long term laxative?
A. Aluminum hydroxide
B. Diphenoxylate
C. lactulose
D. Metoclopramide
E. Mineral oil

21. Your cousin is planning a three-week trip overseas and asks your advice regarding medications for traveler's diarrhea. A drug suitable for non-infectious diarrhea is
A. Aluminum hydroxide
B. Bismuth subcitrate
C. Magnesium hydroxide
D. Metoclopramide
E. Mineral oil

22. Which of the following drugs or drug groups is not useful in the prevention of nausea and vomiting induced by cancer chemotherapy:
A. Dexamethasone
B. Dronabinol
C. Scopolamine
D. Ondansetron
E. Metoclopramide

23. A patient presents with Zollinger-Ellison syndrome due to a gastrinoma. He has two bleeding ulcers and diarrhea. A drug that irreversibly inhibits the H+/K + ATPase in gastric parietal cells is
A. Cimetidine
B. Cisapride
C. Glycopyrolate
D. Omeprazole
E. Ondansetron

24. A drug that is recently linked with some cases of cardiac arrhythmias and sudden death is:
A. Aluminum hydroxide
B. Lactulose
C. Loperamide
D. Ranitidine
E. Domperidone

25. One recognized advantage of domperidone over metoclopramide as a prokinetic agent is:
A. More prominent antiemetic action
B. More powerful stimulant of GIT motility
C. Less CNS adverse effects.
D. Less incidence of diarrhea
E. Less cardiac adverse effects

26. A cannabinoid receptors agonist that is useful for prevention of nausea and vomiting due to cancer chemotherapy is:
A. Dronabilone
B. Morphine
C. Diphenoxylate
D. Naloxone
E. Ondansetron

27. A pregnant woman with 28 weeks gestation complaining of distressing constipation. Which of the following drugs can be prescribed safely?
A. Ondansteron
B. Lactulose
C. Senna
D. Magnesium sulphate salt
E. Castor oil

28. Bisacodyl frequently can cause:
A. Abdominal cramps
B. Constipation
C. Skin rashes
D. Dizziness
E. Nauseas

29. Patients with acute bleeding due to ruptured esophageal varices could be managed by:
A. i.v. terlipressin
B. i.v. sodium bicarbonate
C. Oral lanzoprazole
D. i.v. hydrocortisone
E. Oral lactulose

30. A patient being cared for by the gastroenterology service is being treated with sulfasalazine. Which of the following is the most likely purpose for which it is being given?
A. Antibiotic-associated pseudomembranous colitis
B. E. coli–induced diarrhea
C. Gastric H. pylori infections
D. Inflammatory bowel disease
E. NSAID-induced gastric ulcer prophylaxis

Answers

1 D	7 A	13 D	19 D	25 C
2 A	8 D	14 E	20 C	26 A
3 B	9 A	15 D	21 B	27 B
4 D	10 D	16 B	22 C	28 C
5 D	11 E	17 E	23 D	29 A
6 B	12 B	18 A	24 E	30 D