Lec 1

Physiology of gastric Secretion

Parietal Cells & Acid Production

Volume: Secretes ~2 liters of HCl/day (pH 1.8–3.5).
Role:
Activates pepsin (digests proteins).
Kills ingested bacteria.

Mechanism of HCl Secretion

- **Proton Pump (H^+/K^+-ATPase):** Pumps H^+ into stomach lumen in exchange for K^+ (uses ATP).
- **Chloride (Cl^-) Secretion:** Cl^- exits via apical channels and combines with $H^+ \rightarrow$ HCl in lumen.
- **Bicarbonate (HCO_3^-) Exchange:** HCO_3^- is pumped into blood (alkaline tide) in exchange for Cl^-.

Stimulants of acid secretion

- **Ach from enteric neurons that results in the secretion of pepsinogen.**
- **Histamine from ECL (enterochromaffin - like) cells.**
- **Gastrin released by G cells.**

Inhibitors of acid secretion

Somatostatin in D cells inhibits acid secretion.

phases in gastric acid secretion

Cephalic Phase

the major effect of **gastrin** is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

Gastric Phase

Food stretch stomach walls activating a neural reflex to stimulate acid secretion.
Peptides & amino acids stimulate G cells to release **gastrin**.
Food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion .

Intestinal Phase

Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer

Definition

A defect in the lining of the stomach or the duodenum.

Causes of Peptic Ulcer

- **Helicobacter pylori (most common).**
- **Drugs such as aspirin & other NSAIDs**
- **Smoking**
- **Stress**
- **alcohol**
- **Gastrinomas**
- **Zollinger Ellison syndrome**

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

Symptoms

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

Complications of peptic ulcer

- **Gastrointestinal bleeding. can be life threatening**
- **Cancer**
- **Perforation (hole in the wall) Penetration**

Treatment options

- **Reduce acid secretion /or Neutralize acid in the lumen**
- **Protect the mucosa from acid destruction**
- **Antibiotics to eradicate Helicobacter pylori. If this is successful then the ulcer should begin to heal on its own.**

Acid lowering agents

Antacids

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

Magnesium Hydroxide

Magnesium trisilicate
slow-acting antacid

2HCl + Mg(OH)2 ----> MgCl2 + 2H2O

Magnesium antacids have laxative action; diarrhea.(M D)
ionic magnesium stimulates gastric release
(acid rebound)

Aluminum Hydroxide

AL(OH)3 + HCl -----> ALCl3 + H2O

• Aluminum salts cause constipation.

Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).
~~ Contraindicated in renal insufficiency.
• React slowly and without gas formation.
• Metabolic alkalosis is also uncommon.

Calcium carbonate

2HCl + CaCO3 ---> CaCl2 + **CO2** + H2O

associated with "**acid rebound**"
with excessive chronic use, it may cause **milk-alkali** syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels.

Sodium bicarbonate

NaHCO3 + HCl → NaCl + H2O + **CO2**

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

H2 antagonist

Proton pump inhibitors

Acid lowering agents

Antacids

Proton pump inhibitors

H2 antagonist

Selective competitive inhibitors of the parietal cell H2 receptor and suppress basal and meal- stimulated acid secretion in a dose-dependent manner.
Also decrease volume of secretion and pepsin concentration.

H_2-Receptor Blockers

- Cimetidine, prototype, many problems.
- Ranitidine.
- Famotidine.
- Nizatidine

- 50% first-pass metabolism bioavailability
  نصف الجرعة فقط توصل للدم بسبب هذه العملية
- has little first-pass metabolism
  تقريبًا كل الجرعة تدخل الدم

MOA

- Decrease secretion stimulated by:
- Histamine.
- Gastrin.
- Acetylcholine.
- Duration of action: 12 hours.
- Inhibit:-

60-70% of total 24-h acid secretion.
90% of nocturnal acid.
“Nocturnal acid is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes”
60% of day-time, meal stimulated, acid.

Clinical Uses

1• Gastroesophageal Reflux:
* Prophylactically, before meals.
* Afford healing for erosive esophgitis in less than 50% of patients.
=> Proton pump inhibitors are preferred.
2• Non Ulcer **Dyspepsia**.
3• Stress- Related Gastritis => Can prevent bleeding, usually given IV.
4• In Peptic Ulcer Disease:
… It’s Replaced by PPI.
… Healing rate greater than 80- 90% after 6-8 weeks.
… **Not** effective in the presence of H.pylori infection.
… **Not** effective if NSAID is continued

Adverse Effects

Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation.

CNS

Confusion, hallucinations occur only with IV cimetidine to elderly patients in ICU.

Endocrine Effects

Again only with cimetidine, can inhibit estradiole metabolism, الجسم ما بيقدر يتخلص من هرمون الإستروجين بشكل طبيعي
and can increase prolactin serum levels.(could cause gynecomastia)

Pregnancy and Nursing Mothers

Can cross placental barrier and appear in breast milk.

Others

bradycardia and hypotension

Drug Interactions

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

Lec 2

Acid lowering agents

Antacids

H2 antagonist

Proton pump inhibitors

Proton Pump Inhibitors

- Omeprazole (oral).
- Rabeprazole (oral).
- Lanzoprazole (oral and IV).
- Pantoprazole (oral and IV).
- Esmoprazole (oral and IV).

• Formulated as a prodrug which is released in the intestine.

• Immediate Release Suspension results in rapid response.

Suspension = شكل سائل من الدواء،

Pharmacokinetics

• They are **lipophilic weak bases (pKa 4-5).**

• After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus.

• The prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells.

• There, it undergoes a molecular conversion to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.

=> Rabeprazole has immediate release omeprazole have faster onsets of action.

• Should be given one hour **before** meal.

• Have short half lives but effect lasts for 24 hours due to **irreversible inhibition.**

Pharmacodynamics

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

Clinical Uses

1• Gastroesophageal Reflux:

They are the most effective agents in all forms of GERD and complications.

2• Non Ulcer **Dyspepsia**.

** Modest activity.

** 10-20% more beneficial than a placebo.

3• Stress- Related Gastritis =>

• Oral immediate- release **omeprazole** administered by nasogastric tube.

• For patients without a nasogastric tube, **IV H2-antagonists** are preferred because of their proven efficacy.

4 • Gastrinoma and other Hypersecretory Conditions

Usually high doses of **omeprazole** are used.

5• In Peptic Ulcer Disease:

They heal more than 90% of cases within 4-6 weeks.

H.pylori- associated ulcers

PPI eradicate H.pylori by direct antimicrobial activity and by lowering MIC of the antibiotics.(the lowest dose to kill this micro)

Triple Therapy:

• PPI twice daily.

• Clarithromycin 500mg twice daily.

• Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.

NSAID-associated ulcers

• PPIs promote ulcer healing despite continued NSAID use.

• Also used to prevent ulcer complications of NSAIDs.

Rebleeding peptic ulcer

• Oral or IV.

• High pH may enhance coagulation and platelet aggregation.

Adverse Effects

General:

• Diarrhea, headache, abdominal pain, not teratogenic in animals, but **not** used in pregnancy.

• Reduction of cyanocobalamine absorption. (Vitamin B12 can help balance immune responses to better fight viral and bacterial infections)

• Increased risk of GI and pulmonary infection.

• Increased serum gastrin levels

• Hyperplasia of ECL cells.

• Carcinoid tumors in rats.

• Increase proliferative rate of colonic mucosa.

• Chronic inflammation in gastric body.

• Atrophic gastritis and intestinal metaplasia.

Drug Interactions

• May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.

• Omeprazole can inhibit metabolism of drugs such as diazepam and phenytoin.

• Rabeprazole and pantoprazole have **no** significant interaction.

Drugs Affecting GI Motility

Laxative Agents.

Nonpharmacologic Remedies

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

Bulk-Forming Laxatives

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

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

Stool Surfactant Agents(Softeners)

- They permit water and lipids to penetrate.
- Given orally or rectally.
  - Docusate
  - Glycerin suppository
  - Mineral oil
- Aspiration can cause lipoid pneumonia.
- Can impair absorption of fat-soluble vitamins

Osmotic Laxatives (Purgatives)

- Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid
  - Magnesium oxide (Milk of Magnesia)
    - Can cause **hypermagnesemia**.
    - Large doses of magnesium citrate and sodium phosphate can cause Purgation: rapid bowel evacuation within1-3 hours. This might cause **volume depletion**.
  - Sorbitol
  - Lactulose
    - Sugars metabolized by bacteria producing severe flatus and cramps
  - Balanced Polyethylene Glycol
    - Safe solution: no intrvascular fluid or electrolyte shifts. Does not cause cramps or flatus.
    - Used for complete colonic cleansing before endoscopy.
    - PEG is an inert, nonabsorbable, osmotically active sugar.
    - For colonic cleansing, it should be ingested rapidly(4 L over 2-4hs).
    - For chronic constipation, PEG powder is mixed with water or juice.

Stimulant Laxatives (Cathartics)

- Direct stimulation of the enteric system.
- Colonic electrolyte and fluid secretion.

Adverse effects:- Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.

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

بنعطيها للناس اللي عندهم مشاكل في الأعصاب (يعني أمعاؤهم ما بتتحرك منيح).
كمان بنعطيها للناس اللي نايمين بالفراش لفترة طويلة (مثل المرضى في دور الرعاية).
لأنهم ما بيتحركوا كتير، فأمعاؤهم بتكسل، فبنحتاج شي "ينبّهها" تتحرك وتشتغل.

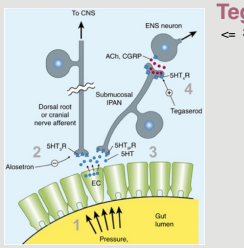
- Anthraquinone Derivatives
  - Aloe
  - Senna
  - Cascara
  - Poorly absorbed .
  - After hydrolysis, produce bowel movement in (6-12) hours.
  - Cause brown pigmentation of the colon" Melanosis Coli".
  - Not carcinogenic
- Castor oil
  - Hydrolyzed in upper intestine into ricinoleic acid which is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

Antidiarrheal Agents

Tegaseroid

مشان نعرف الـ MOA الـ ، لازم نعرف الحالة الطبيعية بالبداية <=

1. أول شي:
لما الأمعاء تتنفخ (تمتلي بالكل أو الغازات)،
خلايا خاصة فيها اسمها EC cells بتفرز مادة اسمها
(سيروتونين) 5-HT
2. بعدين:
5-HT
بيروح يحفّز نوعين من الأعصاب
✅ النوع الأول:
5-HT3 receptors
موجودين على أعصاب بتوصّل للدماغ، لما يتنشّطوا ممكن يصير:
وجع بطن / غثيان / استفراغ
✅ النوع الثاني:
5-HT1P receptors
موجودين داخل الأمعاء، على أعصاب اسمها IPANs، هاي الأعصاب بتنشّط (enteric neurons)
إلّي بيؤدي إلى :
حركات الأمعاء (peristalsis) / إفرازات الهضم
3. وأخيرًا:
5-HT4 receptors
كمان موجودين على الأعصاب داخل الأمعاء، لما يتنشّطوا، بيساعدوا الأعصاب تفرز مواد: ACh && CGRP
وهاي المواد بتقوّي حركة الأمعاء أكتر وأكتر.
النتيجة: الأمعاء تتحرك بشكل طبيعي، تدفع الأكل، وتهضم، وتخلّص الفضلات.



Tegaserod:

- Is a serotonin 5-HT4 partial agonist, which are presynaptic receptors of the submucosal intrinsic primary afferent nerves which enhance the release of their neurotransmitters.
- These neurones stimulate proximal bowel contraction(via ACh and substance P) and distal relaxation(via nitric oxide and VIP).
- The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility.
- Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity.

Clinical Uses

- Chronic constipation
- Nonulcer dyspepsia.عسر الهضم بدون قرحة
- Gastroparesis تأخر إفراغ المعدة
- Irritable bowel syndrome.

Adverse Effects

Diarrhea occurs in 9% of patients within days.

Extremely safe drug.
Expensive

Lec 3

Drugs Affecting GI Motility

Laxative Agents.

Antidiarrheal Agents

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

Opioid Agonists

MOA

Inhibit presynaptic cholinergic nerves
→ ↓ peristalsis
→ ↓ mass colonic movements and gastrocolic reflex.
→ ↑ colonic transit time
حتى يُمتص سوائل قدر المستطاع في وقت اكثر
→ ↑ fecal water absorption
———————————
Can have CNS effects and addiction potential.
Usually combined with atropine to reduce dependence

Examples

- Loperamide
  - Does not cross BBB.
  - No analgesic or addiction potential.
- Diphenoxylate
  Can have CNS effects and dependence.

Adsorbents

~ act to absorb bacteria, toxins and fluid.
~ Usually combined, e.g. Kaopectate.
~ Taken far from other medications.
(to avoid absorption of other drugs)

Examples

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

Bile salt-binding resins

Theses drugs can bind bile salts in cases of Malabsorption of bile salts (e. g .after surgical resection), which can cause diarrhea.
Adverse effects:- bloating, flatulence, constipation and fecal impaction. Also, drug and fat malabsorption.

Examples

- Cholestyramine
- Colistipol

vagotomy usually means cutting the branch of the vagus nerve that tells your stomach to secrete gastric acid.
Dumping syndrome is a condition in which food, especially food high in sugar, moves from your stomach into your small bowel too quickly after you eat.
Scleroderma is an uncommon condition that results in hard, thickened areas of skin

Octreotide

Is a synthetic octapeptide “8” with actions similar to somatostatin.
Somatostatin is a 14 amino acid peptide released in the GIT and pancreas as well as from the hypothalamus:
1. Inhibits release of many hormones.
2. Reduces intestinal fluid and pancreatic secretions.
3. Slows GIT motility and gallbladder contraction.
4. Contracts blood vessels.
5. Inhibits secretion of some anterior pituitary hormones.

Clinical uses

- Inhibition of endocrine tumor effects:
  Carcinoid can cause secretory diarrhea and systemic symptoms like flushing and wheezing.
- Diarrhea due to vagotomy or dumping syndrome or and AIDS.
- In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.
- pituitary tumors and GI bleeding.

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

Drugs Used in the Treatment of Irritable Bowel Syndrome

Antispasmodic or Anticholinergic Agents.

- Spasm is not an important symptom in IBS.
- They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.
- At usual low doses, have minimal side effects.

Examples:
- Dicyclomine
- Hyoscyamine

Serotonin 5-HT3-Receptor **Antagonists**

Alosterone

5-HT3 receptors are present in the afferent pain fibers in the extrinsic sensory neurons.
Also present on the terminals of the enteric cholinergic neurons. Centrally, 5-HT3 is involved in the central response to visceral afferent stimulation.

- Selective antagonist of 5-HT3 receptors.
- Has long duration of action.
- Approved for women with severe IBS in whom diarrhea is the prominent symptom.
- Efficacy in men is not established.
- Can cause ischemic colitis, severe constipation requiring hospitalization and surgery(occurs when blood flow to part of the large intestine is temporarily reduced)

Serotonin 5-HT3-Receptor **Agonists**

Tegaserod

- Approved for short term treatment of women with IBS who predominantly have constipation.
- Reduces pain, bloating and hardness of stool.
- Expensive.

Lec 4

Antiemetic Agents

Nausea and vomiting are manifestations conditions including

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

Pathophysiology

Vomiting pathway

Triggering Signals

- Inner ear (motion/balance) → via Cranial Nerve VIII (Vestibulocochlear)
- Gastrointestinal tract (irritation, toxins, distension) → via Cranial Nerve X (Vagus)
- Chemoreceptor Trigger Zone (CTZ) → detects toxins in the blood
- Higher brain centers (e.g., emotions, sights, smells)

↓

Signals converge on:

Nucleus Tractus Solitarius (NTS) in the brainstem; Acts as a central processing hub

↓

Activation of the Vomiting Center(Located in the medulla oblongata), Contains key receptors:

M1 (muscarinic) / H1 (histamine) / 5-HT_3 (serotonin) / NK1 (substance P)

↓

Coordination with other centers:

Respiratory center → adjusts breathing

Salivatory center → increases saliva

Vasomotor center → affects heart rate and BP

Pharyngeal and abdominal muscles → contract to induce vomiting

↓

Vomiting occurs

Reverse peristalsis

Expulsion of gastric contents through mouth

Antiemetic Agents

Serotonin 5-HT3 Antagonists

Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.
Prevent emesis due to vagal stimulation and chemotherapy.
Other emetic stimuli such as motion sickness are **poorly** controlled.
Uses:-
Prevention of 1. acute chemotherapy-induced nausea and emesis and 2. postoperative nausea and vomiting.
Their efficacy is enhanced by combination therapy with dexamethasone and NK1-receptor antagonist.
Adverse effects: Headache, dizziness, and constipation.

Examples:
- Ondansetron
- Granisetron

Neurokinin 1 Receptor (NK1) Antagonists

Aprepitant
Block central NK1receptors in the area postrema. جزء حساس للكيميائيات في الدم
Used in combination with 5-HT3-receptor antagonists and corticosteroids for the prevention of acute and delayed nausea and vomiting from chemotherapy.

Cannabinoids

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.

Examples:
- Dronabinol
- Nabilone

Benzodiazepines

Reduce vomiting caused by anxiety.

Examples:
- Lorazepam
- Diazepam

Antipsychotic drugs

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

Examples:
- Prochlorperazine
- Promethazine
- Droperidol

Lec 5

PROTOZOAL DISEASES

=> Protozoal and helminthic infections are a major cause of disease in many parts of the world.
some of these diseases:-
•in migrant workers
•or individuals returning from an endemic area

Amebiasis

• The protozoan **Entamoeba histolytica** causes amebiasis, an infection that is endemic in parts of the United States.

can be present in the host as

encysted

Initial ingestion of the cyst may result either in 1)no symptoms or in 2)severe amebic dysentery characterized by the frequent passage of bloodstained stools

trophozoite

symptom occurs after invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite
=> Trophozoites may spread to the liver through the portal vein and produce acute **amebic hepatitis**

Entamoeba histolytica can cause

- Asymptomatic intestinal infection.
  - **Treatment**
  - luminal amebicide.
  - Ex
  - **Diloxanide furoate, Iodoquinol, and Paromomycin.**
- Mild to moderate colitis
  - **Treatment**
  1. Metronidazole + luminal amebicide
  2. Tetracyclines and erythromycin — not effective against extraintestinal disease.
  3. Dehydroemetine or emetine — best avoided because of toxicity
- Severe intestinal infection (dysentery)
- Ameboma
- Liver abscess and other extraintestinal infection

Balantidiasis

• The protozoan **Balantidium coli** causes balantidiasis.
•the largest of the protozoans that infect humans

encysted

Infection is acquired through the ingestion of cyst-contaminated soil, food, or water.

trophozoite

trophozoite form is covered with cilia, which impart mobility
• The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine
• healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea
• nutritionally stressed patients may develop severe dysentery.

Classes of oral antiprotozoal drugs

miscellaneous antiprotozoals

metronidazole

Flagyl, Metrogel

Drug of choice in the treatment of extraluminal amebiasis.
It kills trophozoites but not cysts of E histolytica and effectively eradicates intestinal & extraintestinal tissue infections.

MOA

• exerts activity against most anaerobic bacteria and several protozoa.
•The drug freely penetrates protozoal and bacterial cells but not mammalian cells.
•The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug => the Reduced metronidazole disrupts replication and transcription and inhibits DNA repair

Clinical Uses

1. Amebiasis

The drug of choice in the treatment of all tissue infections with E histolytica. (hepatic abscess; intestinal wall/ extraintestinal infections)
• Not effective against luminal parasites and so must be used with a luminal amebicide to ensure eradication of the infection. kills trophozoites but not cysts

2. Giardiasis

Metronidazole is the treatment of choice. Efficacy after a single treatment is about 90%
Tinidazole is equally effective.

3. Trichomoniasis

Metronidazole is the treatment of choice. A single dose of 2 g is effective.

Adverse Effects

Common: Nausea, headache, dry mouth, metallic taste.
Infrequent adverse effects: vomiting, diarrhea, insomnia, weakness, dizziness,.
Rare: Pancreatitis and severe central nervous system toxicity

Cautions

Metronidazole is best avoided in pregnant or nursing women

tinidazole

works as well as metronidazole and has many of the same side effects, but it can be given in a single dose.

nifuratel

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

antimalarial drugs

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

Life Cycle of Malaria Parasites

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

antimalarial drugs

Examples

Chloroquine

•Most useful agent to terminate an acute attack.
•Available as oral, IV, and IM preparation.
•Resistance develops.
•Causes Nausea ,headache, and it is teratogenic.

Quinine

• Oldest drug, from Cinchona tree.
• Many actions
• Toxic
• Still used, no resistance to its action

Artemisinin

• New drug, from Sweet wormwood, الشيح

Doxycycline

Pyrimethamine

Lec 6

Pathogenic helminths

Infection by helminths (worms)
• May be limited solely to the intestinal lumen
Or
•May involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue

helminths life cycle

either

- a simple cycle of egg deposition and development of the egg → to produce a mature worm
- must => progress through one or more hosts and one or => more morphological stages, each *metabolically distinct* from the other, before emerging as an adult

Anthelmintics

either

- act locally to expel worms from the gastrointestinal tract
- systemically to eradicate adult helminths or developmental forms that invade organs and tissues

anthelmintic drugs exert their antiparasitic effects by interference with
- energy metabolism
- neuromuscular coordination
- microtubular function
- cellular permeability

cestodes (flatworms)

general properties
- Flat worms, tape-like, Segmented parasites
- Length range from mm to meters
- Scolex (Head) provided with suckers, Hooks +/-
- Adult worms are in Gastrointestinal tract
- Digestive tract is absent, absorb nutrients from body wall تبعها
- Hermophrodites خنثى
- Reproductive system, Excretory & Nervous systems are present
- complete chain of segments known as strobila, Each Segment is called Proglottid
- Life span - 5 to 25 years

Treatment

Niclosamide

am-chlorinated salicylamide that **inhibits the production of energy** derived from anaerobic metabolism

•Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite.

•The drug affects the scolex and proximal segments of the cestodes => resulting in detachment of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel.

nematodes (roundworms)

•The body of a nematode is long and narrow, resembling a tiny thread in many cases, and this is the origin of the group's name

•Most living roundworms are microscopic, On the other hand, one species of parasitic nematode can reach 13 meters in length

Treatment

1 Piperazine

•Prolonged treatment and might need a purgative

•Piperazine (Vermizine) contains a heterocyclic ring that lacks a carboxyl group.

• acts on the **musculature** of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. this results in expulsion of the worm.

• Piperazine acts as an agonist at gated **chloride channels** on the parasite muscle.

2 Diethylcarbamazine

•It **interferes with the metabolism of arachidonic acid** and blocks the production of prostaglandins

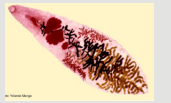
• resulting in capillary vasoconstriction and impairment of the passage of the microfilaria

3 Mebendazole"Vermox"

Widely used, wide spectrum, safe drug.

trematodes (flukes)

الديدان المثقوبة



cause various clinical infections in humans.

•The parasites are so named because of their conspicuous suckers, the organs of attachment

Treatment

Praziquantel "Biltricide"

• **increase parasite motility leading to spastic paralysis.**

•The drug increases **calcium** permeability through parasite-specific ion channels, so that the muscle cells of the parasite accumulate calcium.

=> This action is followed by exposure of hitherto masked tegmental antigens, lipid anchored protein, and actin.

•Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault

بيفتح سطح الطفيلي ويكشف مستضدات كانت مخفية، فالجهاز المناعي بيقدر يتعرف عليه، يرسل أجسام مضادة، ويهاجمه بـ(Complement) ← النتيجة: موت الطفيلي.

أنواع الـ nematodes الي بتعالجهم

- Threadworm
  Enterobius vermicularis, simple teatment: => single dose, can be repeated after 3 weeks.
- Hockworm
  Ankylostomiasis: 2tablets for 3days.
- Roundworm
  Ascaris lumbricoidis

Acanthocephala (thorny- headed worms) مشوكات الرأس

•Thorny-headed worms, are parasites that live in the gut of vertebrates and - earlier in their life cycle - within invertebrates.

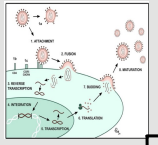
• Acanthocephalans lack a mouth or alimentary canal. Adult stages live in the intestines of their host and uptake nutrients which have been digested by the host, directly, through their body surface

The most common viral infections of the GI tract

- **Viruses** are **obligate intracellular** microbes
- use many of the host cell's biochemical mechanisms and products → to sustain their viability
- A mature virus(virion) can exist outside a host cell and still retain its infective properties.
- the virus must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles

=> Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid).

- Many viruses possess an outer envelope of protein or lipoprotein.



Cytomegalovirus (CMV)

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

Herpes simplex virus (HSV)

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

Adenovirus

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

Rotaviruses

- Rotaviruses are double-stranded RNA viruses in the family Reoviridae.
- They are responsible for common diarrheal illness
- although prevention through **vaccination** is becoming more common.
- The virus is primarily spread by the fecal-oral route

Common in **children**, especially in day-care centers; ~95% of U.S. children infected by age 5.

Adults usually have immunity → asymptomatic or mild infections.

Elderly are vulnerable due to weakened immunity, especially in nursing homes.

Transmission:

Through: - Contact with infected individuals (clinical or subclinical).

- Contaminated surfaces (virus survives for a while).

Symptoms:

Fever, vomiting, diarrhea (appears ~2 days after exposure).

Virus infects epithelial cells of small intestinal villi.

May cause lactose intolerance.

Course:

Illness lasts 3–8 days.

Can lead to: - Severe dehydration, especially without treatment.

- Malnutrition with repeated infections.

Increased risk of death in developing countries

Noroviruses

- Noroviruses, commonly identified as Norwalk viruses, are **caliciviruses**.
- Several strains can cause gastroenteritis.
- There are millions of cases a year, predominately in infants, young children, and the elderly.
- These viruses are easily transmitted and highly contagious.
- They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships.
- The viruses can be transmitted through direct contact, through touching contaminated surfaces, and through contaminated food.
- Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.
- The signs and symptoms of norovirus infection are similar to those for rotavirus,
- with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting.
- The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur.
- Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

diagnosis

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

Treatment

- **No medications** are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used.

Classification of Viruses

either

DNA viruses

- adenoviruses (colds,conjunctivitis)
- hepadnaviruses (hepatitis B)
- herpesviruses (cytomegalovirus chickenpox)
- papillomaviruses (warts)

RNA viruses

- arborviruses (yellow fever)
- arenaviruses (meningitis)
- orthomyxoviruses (influenza)
- paramyxoviruses (measles, mumps)
- picornaviruses (meningitis, colds)
- rubella virus (German measles)
- retroviruses (AIDS)

diagnosis

The most common clinical tool for diagnosis is **enzyme immunoassay**, which detects the virus from fecal samples.

Latex agglutination assays are also used. Additionally, the virus can be detected using **electron microscopy** and RT- **PCR**.

Treatment

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