

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



جناح

GIS Pharmacology | FINAL 5&6

Antiprotozoal pt.2, Anthelmintics & Antiviral drugs



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Classes of oral antiprotozoal drugs

Commonly used oral antiprotozoal drugs can be generally classified into two main groups:

- *antimalarial drugs*
- *miscellaneous antiprotozoals.*

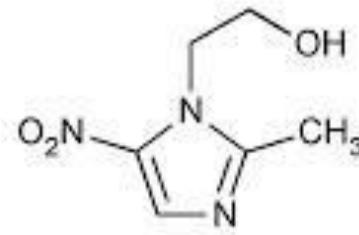
In addition to their use as antiprotozoals, some of them such as metronidazole and doxycycline are also used for treating bacterial infections.

antiprotozoals

Commonly used miscellaneous antiprotozoals include

- metronidazole, **Most famous**
- tinidazole and
- nifuratel.

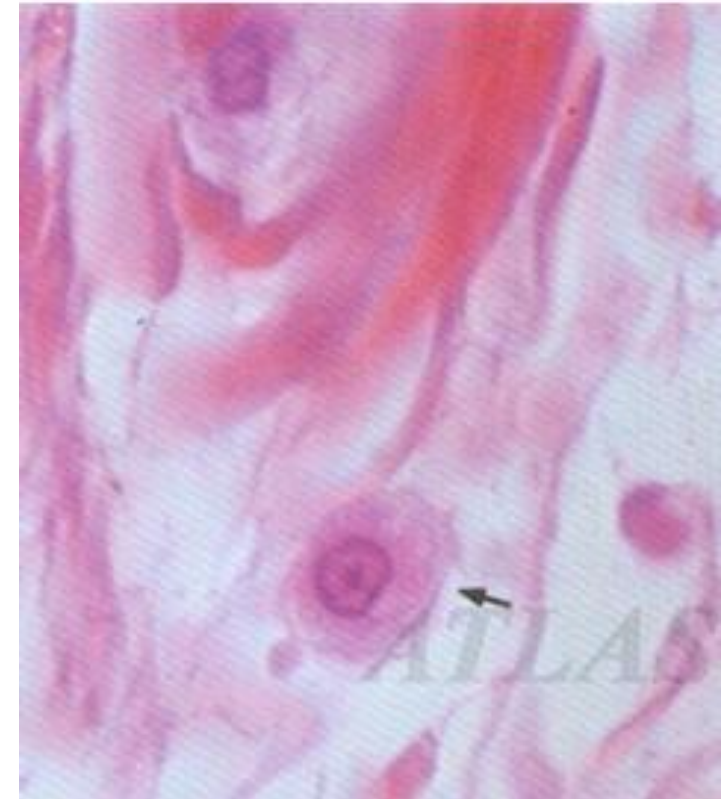
Metronidazole



The chemical structure

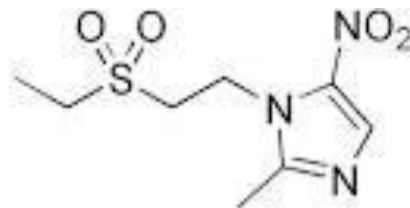
Drug of choice in the treatment of extraluminal amebiasis.

It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal & extraintestinal tissue infections.



Trophozoite of *Entamoeba histolytica* in intestine.

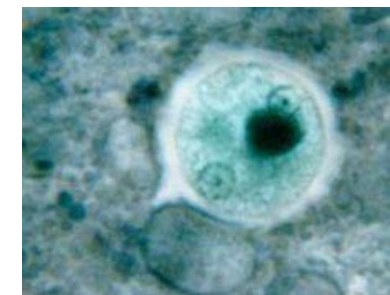
Tinidazole



Similar activity

& better toxicity profile than metronidazole.

So it is described for more complicated cases



cysts of *E histolytica*

Metronidazole

- Metronidazole (*Flagyl, Metrogel*)
- exerts activity against most anaerobic bacteria and several protozoa.

- The drug freely penetrates protozoal and bacterial cells but not mammalian cells.

Metronidazole

- The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug.
- Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

Clinical Uses

Amebiasis

Metronidazole

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

Giardiasis

Metronidazole is the treatment of choice

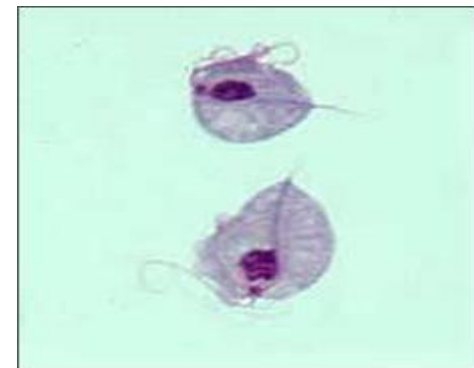
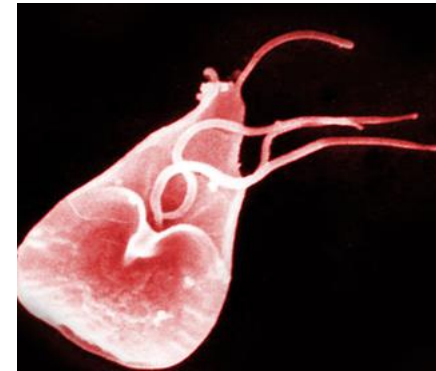
Efficacy after a single treatment is about 90%

Tinidazole is equally effective.

Trichomoniasis

Metronidazole is the treatment of choice.

A single dose of 2 g is effective.



Trichomonas vaginalis

Adverse Effects & Cautions

Common:

Nausea, headache, dry mouth, metallic taste. **Not a serious side effect**

Infrequent adverse effects:

vomiting, diarrhea, insomnia **if it affect the CNS**, weakness, dizziness,.

Rare:

Pancreatitis and severe central nervous system toxicity Tinidazole is better tolerated.

Metronidazole is best avoided in pregnant or nursing women, although congenital abnormalities have not clearly been associated with use in humans.

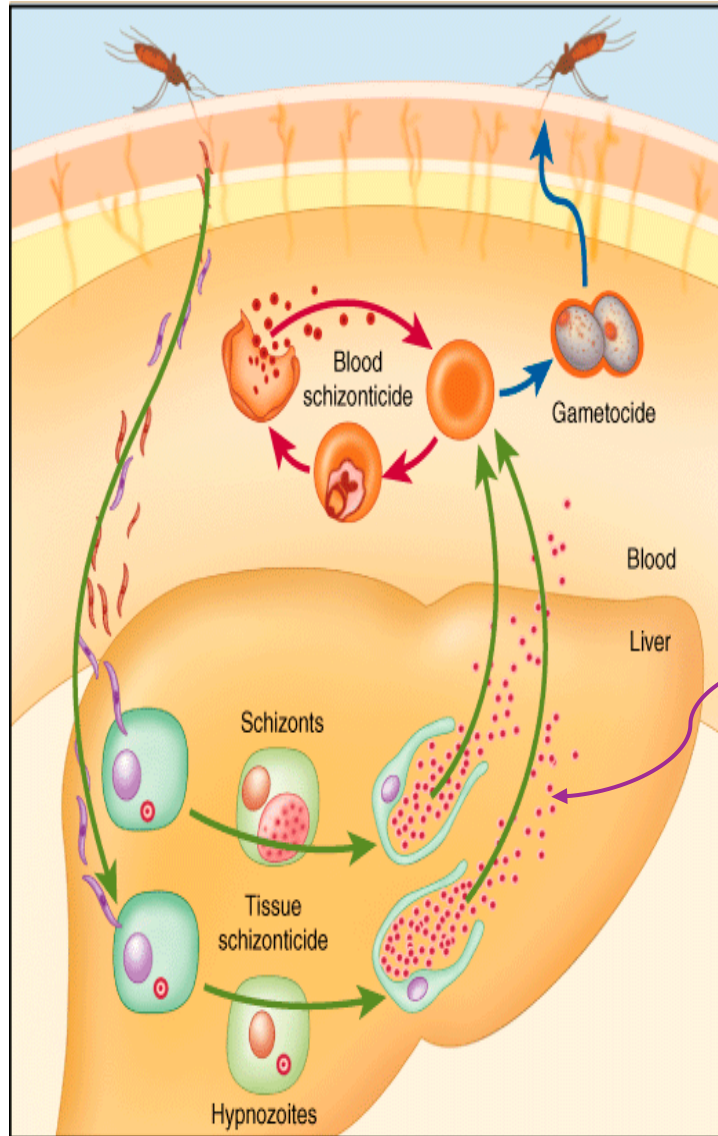
Tinidazole

Tinidazole works as well as metronidazole and has many of the same side effects **except in CNS effect** ,but it can be given in a single dose. Whereas, 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

- **Chloroquine:**
 - **Most useful agent to terminate an acute attack.**
 - **Available as oral, IV, and IM preparation.** *It depends on patient state*
 - **Resistance develops.**
 - **Causes N, headache, and is teratogenic.**

It may be given if the mother's condition is severe, where the mother's life takes priority over the fetus.

Antimalarial Drugs

- **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**

Although it's an antibiotic it possesses an antimalarial effect, however bacterial resistance should be taken into account since it's an antibiotic

Anthelmintics :are infections caused by helminths.

Infection by *helminths* (worms)

- May be limited solely to the intestinal lumen
- May involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue.

helminths have either

- a simple cycle of egg deposition and development of the egg to produce a mature worm,
- others must progress through one or more hosts and one or more morphological stages, each metabolically distinct from the other, before emerging as an adult (More complex than the previous)

Pathogenic helminths can be divided into the following

- *cestodes* (flatworms),
- *nematodes* (roundworms),
- *trematodes* (flukes)
- *Acanthocephala* (thorny-headed worms).

CESTODES : general properties

- Flat worms, tape-like, Segmented parasites
- Length range from mm to meters
- Scolex (Head) provided with suckers, Hooks +/- that attach to the intestinal tract.
- Adult worms are in Gastrointestinal tract
- Digestive tract is absent, absorb nutrients from body wall of the intestine.
- Hermaphrodites, Reproductive system, Excretory & Nervous systems present
- complete chain of segments known as **strobila**, Segment – **Proglottid**
- Life span – 5 to 25 years

Another stage is

Segments development happens in stages:

- 1) Immature proglottids
- 2) Mature (Hermaphroditic) proglottids
- 3) Gravid proglottids



Nematode the 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 (**Wide range**)



Trematodes

الديدان المثقوبة

- Trematode infections occur worldwide.
- Trematodes, also called flukes, cause various clinical infections in humans.
- The parasites are so named because of their conspicuous suckers, the organs of attachment, also used for nutrients absorption.

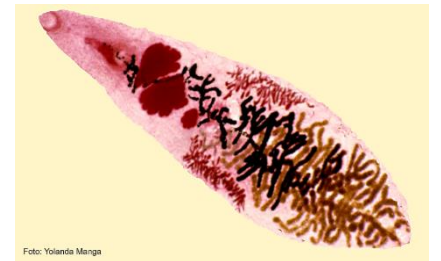
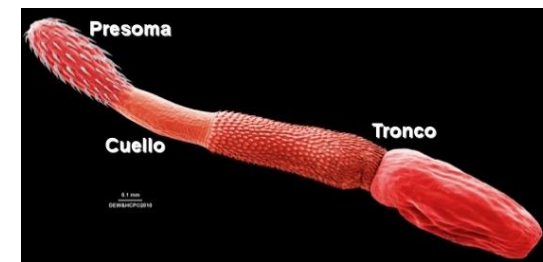


Foto: Yolanda Manga

مشوكات الرأس *Acanthocephala*

- 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.

Due to the absence of a digestive tract they can only feed on already-digested food.



Anthelmintics

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

Most available anthelmintic drugs exert their antiparasitic effects by interference with :

- (1)energy metabolism,
- (2)neuromuscular coordination,
3. microtubular function
4. cellular permeability

They work through different mechanisms of action

TREATMENT FOR INFECTIONS CAUSED BY NEMATODES

Piperazine

Usually not sufficient on its own that's why it might need a purgative to expel the worms outside the body.

- Prolonged treatment and might need a purgative
- Piperazine (Vermizine) contains a heterocyclic ring that lacks a carboxyl group. *Which will interfere with its pharmacological work.*

Piperazine

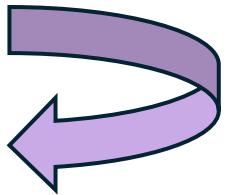
- It acts on the musculature of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. this results in expulsion of the worm.
- Piperazine acts as an agonist at gated chloride channels on the parasite muscle.

"وعسى أن يأذن ربنا لدعواتنا فتكُن"

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

Which results in the eradication of the worms.



Most famous one

Mebendazole”Vermox”:

- Widely used, wide spectrum, safe drug.
 - Threadworm: *Enterobius vermicularis*,
simple treatment:
single dose, can be repeated after 3 weeks.
- Hookworm: *Ankylostomiasis*:
2tablets*3days.
- Roundworm: *Ascaris lumbricoidis*

TREATMENT FOR INFECTIONS CAUSED BY CESTODES

Niclosamide

- Niclosamide is amchlorinated 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 *So the parasite is eradicated due to inhibition of its energy production.*

Niclosamide

- 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.

Helping in eradicating the worm

TREATMENT FOR INFECTIONS
CAUSED
BY TREMATODES

Praziquantel

- The neuromuscular effects of praziquantel (Biltricide) appear to 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

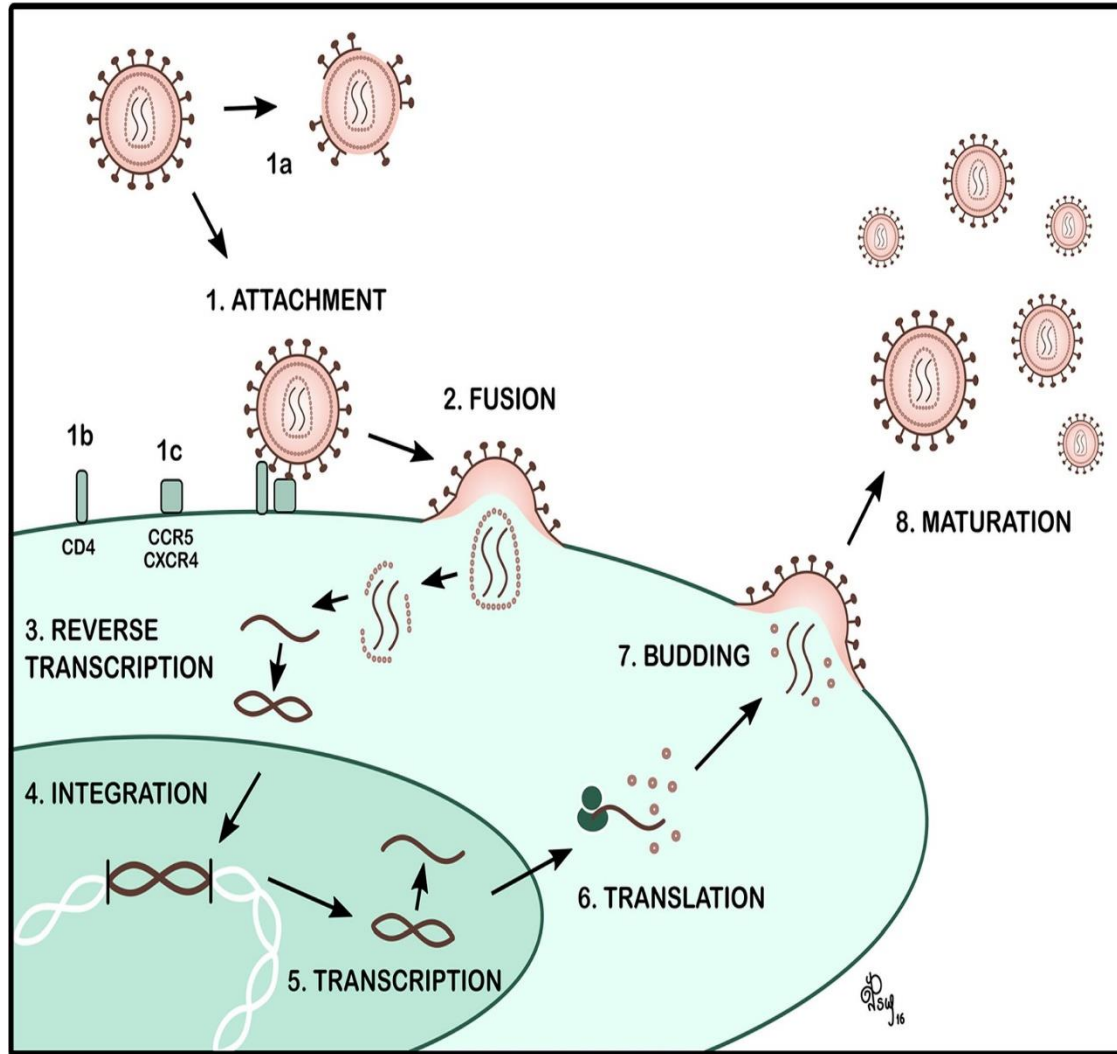
Praziquantel

- 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.

Antiviral Agents

The doctor skipped a few slides
and started directly from CMV

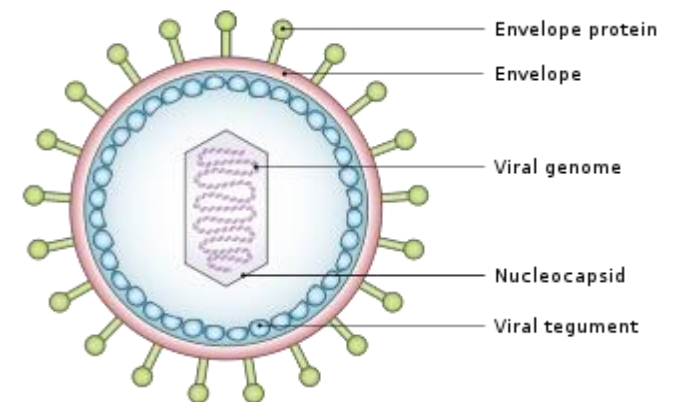
- Viruses are obligate intracellular microbes
- use many of the host cell's biochemical mechanisms and products to sustain their viability
- A mature virus(virion) can exist outside a host cell and still retain its infective properties.



- 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

Classification of Viruses

- **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.**
- **Viral cores can contain either DNA or RNA**



- **viruses may be classified as DNA viruses or RNA viruses.**
- **Further classification is usually based on morphology, cellular site of viral multiplication, or other characteristics.**

- **DNA viruses**
- **adenoviruses (colds, conjunctivitis)**
- **hepadnaviruses (hepatitis B);**
- **herpesviruses (cytomegalovirus**
- **chickenpox)**
- **papillomaviruses (warts)**

- RNA viruses
- arboviruses (yellow fever)
- arenaviruses (meningitis);
- orthomyxoviruses (influenza);
- paramyxoviruses (measles,
- mumps);
- picornaviruses (meningitis, colds);
- rubella virus (German measles)
- retroviruses (AIDS).

Antiviral Agents

- Viruses live intracellular,
- so drugs should be able to enter the human cells.

**The most encountered viral
infections of the GI tract**

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. *But the effect will be less*
- 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. *If it occurs it needs hospitalization*

Gastroenteritis Caused by Rotaviruses

- Rotaviruses are double-stranded RNA viruses in the family Reoviridae.
- They are responsible for common diarrheal illness
(It occurs in both pediatric and elderly patients)
- although prevention through vaccination is becoming more common.
- The virus is primarily spread by the fecal-oral route

- These viruses are widespread in children, especially in day-care centers.
- The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.
- Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection (**this makes the virus controllable**) or, if they do, are asymptomatic.

- The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age,
- so infections can spread through nursing homes and similar facilities.
- In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease.
- The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

- Infected individuals exhibit fever, vomiting, and diarrhea.
- The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi.
- Infection can cause food intolerance, especially with respect to lactose.
- The illness generally appears after an incubation period of about two days and lasts for approximately one week (three to eight days).
- Without supportive treatment, the illness can cause severe fluid loss, dehydration, and even death.

- Even with milder illness, repeated infections can potentially lead to malnutrition, especially in developing countries,
- where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water.
- Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their risk of death from rotavirus infection.

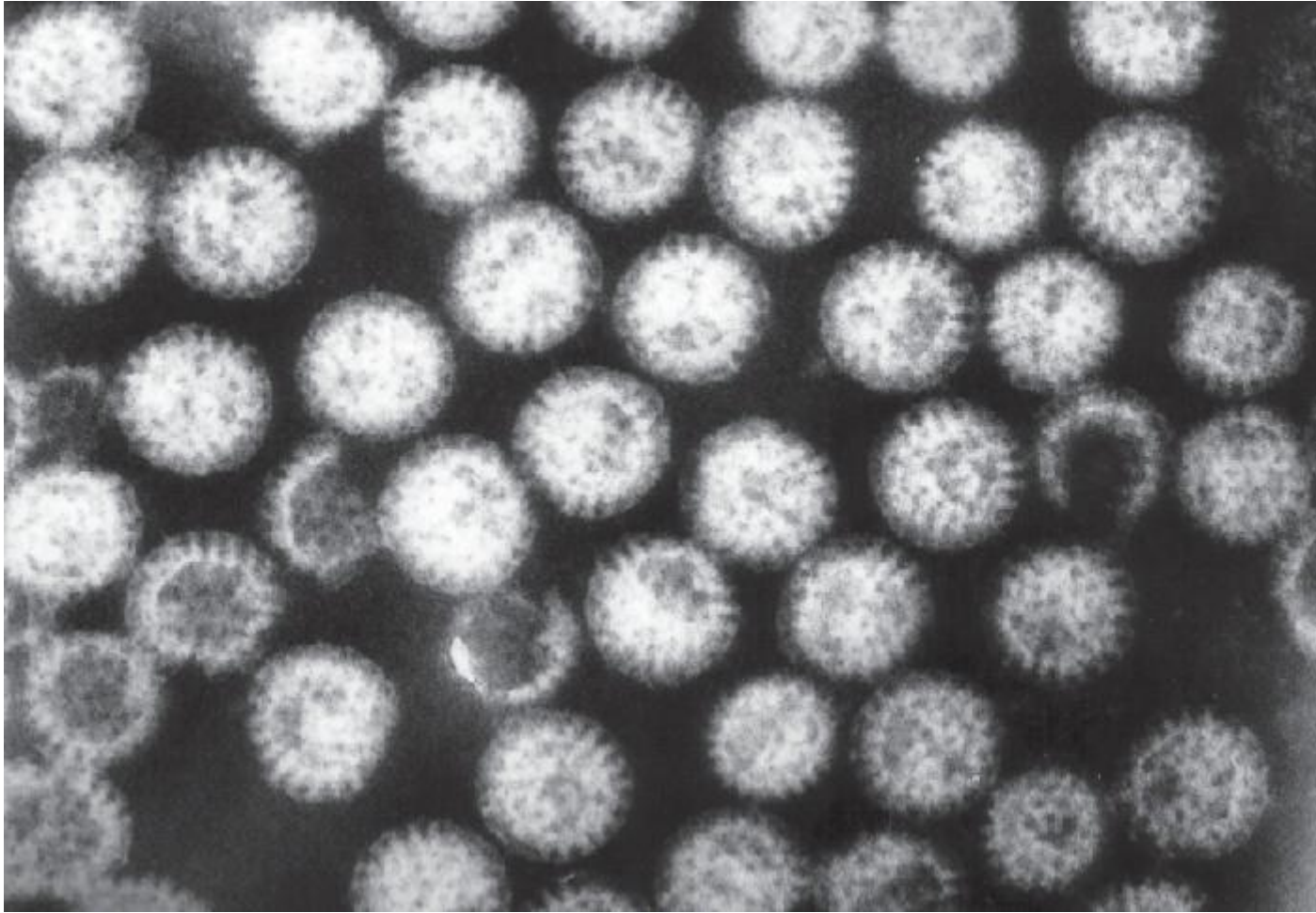
Diagnosis

- 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.

RT-PCR is the most accurate and preferred method.

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.



Rotaviruses in a fecal sample are visualized using electron microscopy

Gastroenteritis Caused by 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.

- 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.
- No medications are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used.
- Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

The table is required but don't worry it's a summary for what has been previously mentioned

Viral Causes of Gastroenteritis					
Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Vaccine
Norovirus gastroenteritis	Noroviruses	Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days	Highly contagious via direct contact or contact with contaminated food or fomites	Rapid enzyme immunoassay confirmed with RT-qPCR	None
Rotavirus gastroenteritis	Rotaviruses	Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death	Fecal-oral route; children and elderly most susceptible	Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR	Preventive vaccine recommended for infants

You should know that fever and diarrhea are common between the two illnesses also notice how Noroviruses can be transmitted through clean surfaces (not contaminated with feces) unlike Rotavirus.

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