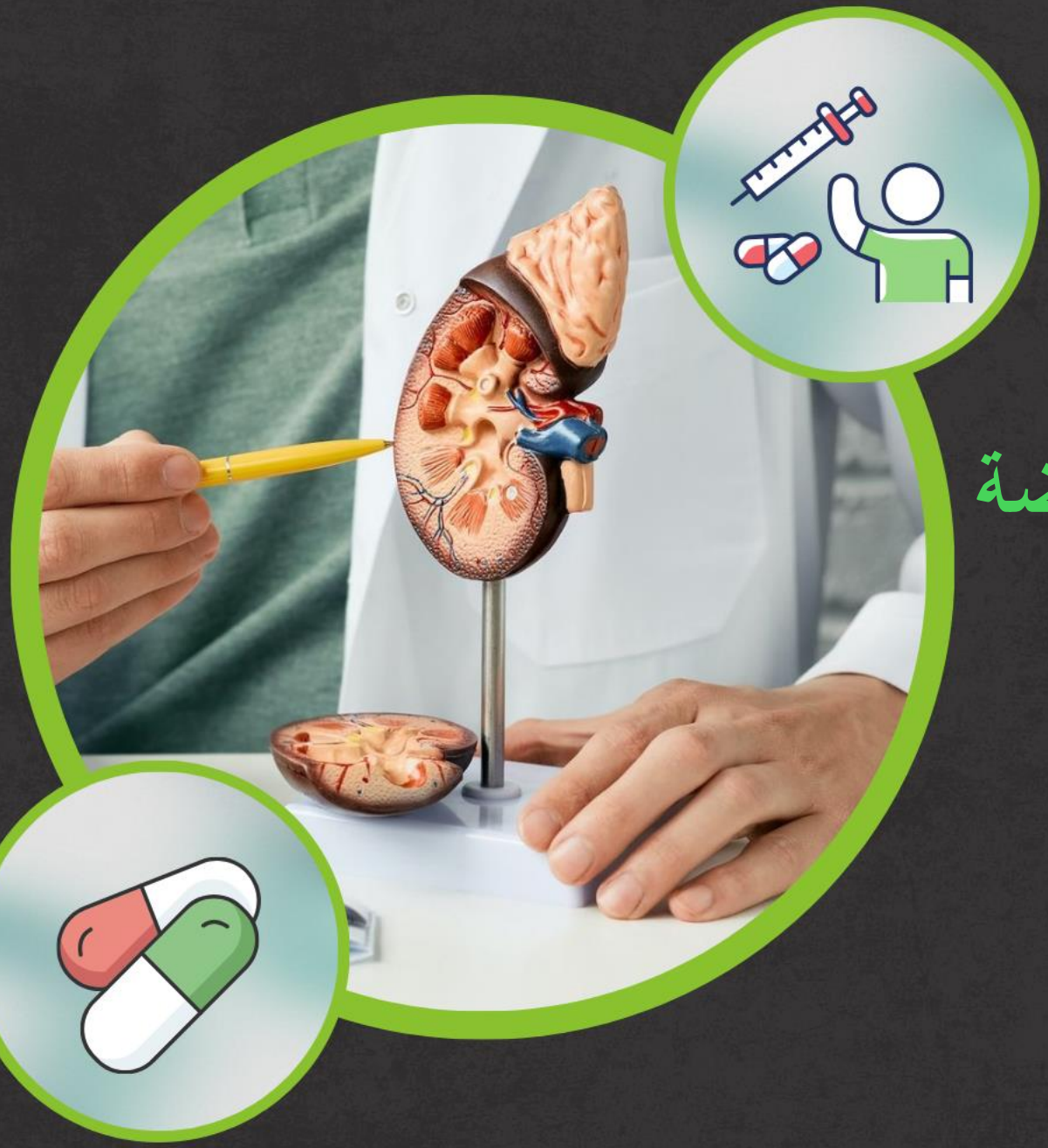


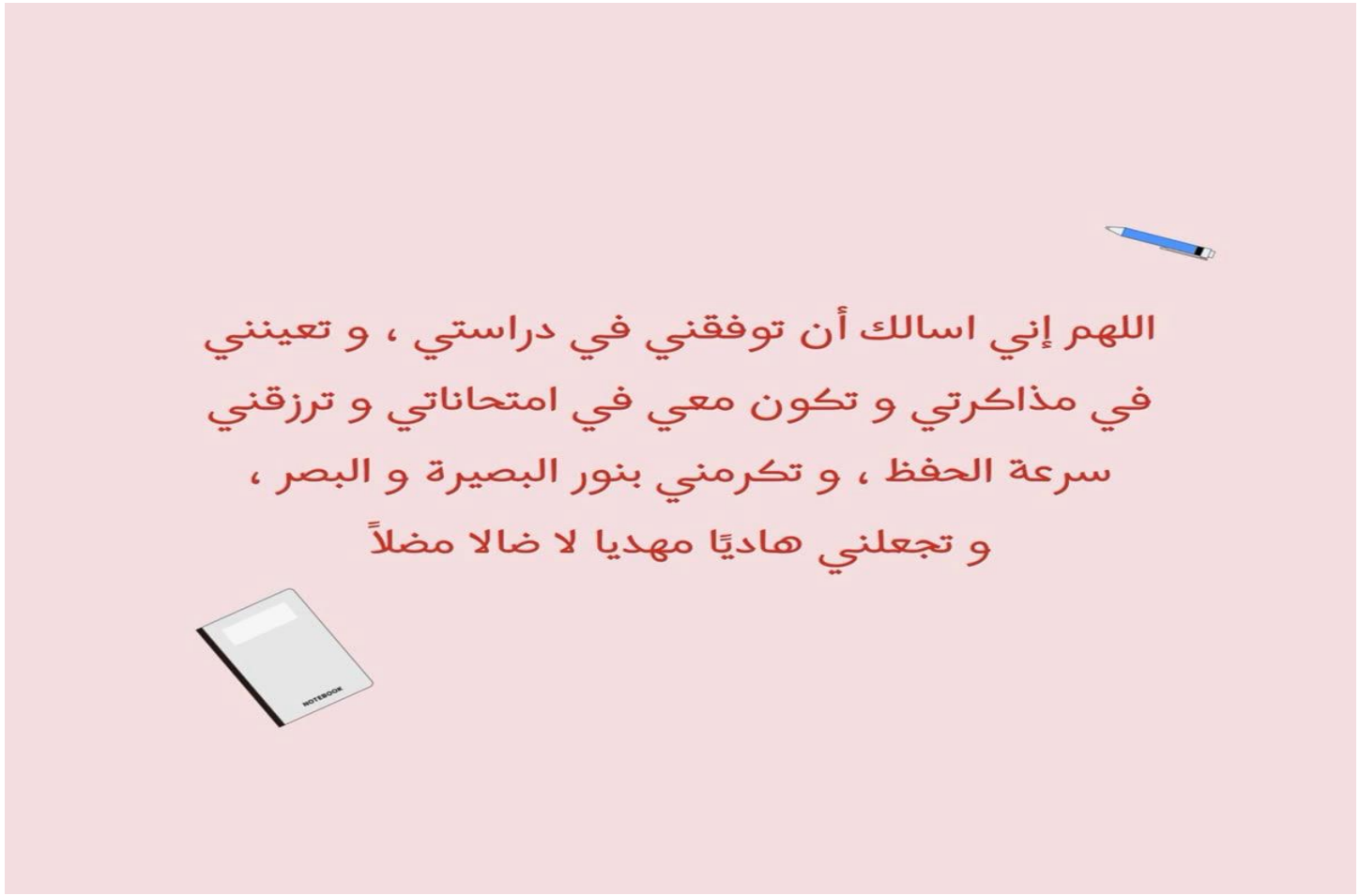
PHARMA

MODIFIED NO. 6

الكُتّاب: حلا موسى-إسماعيل العارضة

المدققين: تم التدقيق

الدكتور/ة: يعقوب إرشيد



Color code

- Slides
- Doctor
- Additional info
- Important

Drugs for Genital Infections

Yacoub Irshaid MD, PhD, ABCP

->We have a few drug we will talk about it, the first one is metronidazole that is an antiprotozoal drug used for ameba ,giardia and trichomonas and so on ,but it is also useful for anaerobic bacterial infection.
->It has another little brother called tinidazole and both are nitroimidazoles.
Note: MOA >> Reduction of the nitro group is responsible for antimicrobial activity.

Extra

Nitroimidazoles are a class of **antimicrobial and antiparasitic compounds** characterized by the presence of a **nitro group (-NO_2) attached to an imidazole ring**. They are primarily used to treat **anaerobic bacterial infections and protozoal infections**.

Key Points:

- **Structure**: Imidazole ring with a nitro group (NO_2).
- **Mechanism of Action**: Nitroimidazoles are **prodrugs** activated in **anaerobic conditions**. The nitro group is reduced inside anaerobic organisms to produce **reactive intermediates** that damage DNA, leading to cell death [1].
- **Spectrum**: Active primarily against **anaerobic bacteria** (e.g., *Bacteroides*, *Clostridium*) and **protozoa** (e.g., *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis*).

Common Nitroimidazoles:

1. **Metronidazole** – most widely used; treats bacterial vaginosis, trichomoniasis, amoebiasis, giardiasis, and anaerobic infections.
2. **Tinidazole** – similar to metronidazole but with a longer half-life.
3. **Secnidazole** – newer, single-dose treatment for bacterial vaginosis and trichomoniasis.
4. **Ornidazole** – used in some countries for protozoal and anaerobic infections.

Medical Uses:

- **Gastrointestinal infections** (e.g., *Clostridioides difficile*)
- **Pelvic infections**
- **Dental abscesses**
- **Surgical prophylaxis**
- **Protozoal diseases** like amoebiasis and giardiasis

Metronidazole

- **Metronidazole and tinidazole are nitroimidazoles.**

Mechanism of Action:

- **The nitro group of metronidazole is chemically reduced in anaerobic bacteria and sensitive protozoans.**
- **Reactive reduction products appear to be responsible for antimicrobial activity.**

Metronidazole

Pharmacokinetics:

- **Oral metronidazole and tinidazole are readily absorbed and permeate all tissues by simple diffusion.** Very important
- **Intracellular concentrations rapidly approach extracellular levels**
- **Peak plasma concentrations are reached in 1–3 hours.** Not delayed (fast)
- **The half-life of unchanged drug is 7.5 hours for metronidazole and 12–14 hours for tinidazole.**

- the in plasma and intracellular compartment are equal and few drugs will have that.
- in a certain infection that are caused by intracellular microorganisms, we need the drug to enter the cell as in tuberculosis treatment, we use a multiple drugs because we have a different population of pathogens in lung are intracellular (in macrophages) and they are a source of infection later on and contribute to the current infection also ,so we need the drugs to enter macrophages and there is no single anti TB drug can enter all these sites for mycobacteria.
- We can give metronidazole IV ,but not for a single infection because the severe adverse reactions of the drug like GI effects.
- We increase the dose when we give it IV to the patient , we give the patient 4 times a day instead of 3 because of the reduction of the liver, when we give the IV drug ,it will distribute equally to all organs like liver and kidney ,but when we give it orally ,it directly goes to the liver before reaching the systemic circulation.
- When we talk about the treatment of ameba, we need to give 500-750 mg/8 hours in metronidazole for 10-14 days. In tinidazole, we treat it for 3 days in regardless to the dose because it's long half life.
- This have advantages and disadvantages:
- Advantages: the patient instead of taking the drug 3 times a day, he will take it every 3 days.
- The disadvantages: there adverse effects, he will end earlier with metronidazole and will last longer with tinidazole.

Metronidazole

- **Can be given PO(orally), PR(in the rectum), Topical & IV.**
- **Metronidazole and its metabolites are excreted mainly in the urine.**
- **Plasma clearance of metronidazole is decreased in patients with impaired liver function.**

So, we reduce the dose in impaired hepatic function.
We have 4 types for this condition:
1- we don't change the dose regardless it's liver state.
2- we reduce the dose if the patient has a liver disease.
3- we reduce the dose if the patient has a renal disease.
4- we make a combination when the patient has liver and renal disease we reduce the dose in both because the drug is partially metabolized in the liver and partially in the kidney.

Metronidazole

- Therapeutic Uses:

1. Bacterial vaginosis: caused by anaerobic bacteria that flares in the absence of the normal flora, *Gardnerella vaginalis, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina.

   - These bacteria are more specific to the vagina.
   - It is a sexually transmitted disease between husband and wife, the husband will get infected without symptoms and if you treat the wife alone, she would be susceptible to a recurrent infection.

2. Trichomoniasis – in the vagina and other places.

Metronidazole

Other therapeutic uses:

A. **Invasive amebiasis in the intestine and liver, but less effective against organisms in the lumen of the gut. They kill the trophozoites of *Entameba histolytica* with no effect on cysts (which is present in the lumen of GI).**

B. **Giardiasis**

The treatment is a one dose single 500 or 750mg will treat watery diarrhea.
It is transmitted feco-orally.

There are available amebicide called diloxanide and it isn't present in our region ,but we have an alternative which is doxycycline ,but it isn't effective as diloxanide.

C. **Anaerobic bacteria: *Bacteroides fragilis, Clostridium spp*** (which is make a super infection pseudomembranous colitis)**& some streptococci. Intraabdominal infections, Antibiotic-associated enterocolitis and brain abscess.**

Metronidazole

Adverse Effects:

1. **Metallic, bitter taste, nausea & dry mouth.**
2. **GIT irritation: vomiting, diarrhea.**
3. **Irritation of mucous membranes – dysuria** (difficult or painful urination), **dark urine.**
4. **Rash and neutropenia** **(allergy).**
5. **Alcohol intolerance: disulfiram-like reaction** (inhibition of acetaldehyde dehydrogenase which make accumulation of acetaldehyde in alcoholics).
6. **Pancreatitis.**
7. **IV infusion may be associated with seizures and peripheral neuropathy.**

Metronidazole

8. **CNS: dizziness, insomnia, weakness, headache, sensory neuropathies, parasthesia, ataxia, encephalopathy, seizures. Use with caution in CNS disease.**
9. **Needs dose adjustment in severe hepatic or renal disease.**
10. **Better avoided during pregnancy and lactation.**

It is teratogenic due to reactive products.

Metronidazole

Drug Interactions:

1. **It potentiates the anticoagulant effect of warfarin.**
2. **Elimination is accelerated by phenobarbital and phenytoin and inhibited by cimetidine.**
3. **May increase lithium toxicity.**

Due to renal excretion, it decrease lithium excretion and it will be accumulated which will increase the toxicity.

📌 Another drug that's used for anaerobic bacterial infections:

Clindamycin

Mechanism of Action:

- **Inhibits microbial protein synthesis, by interfering with the formation of initiation complexes, and with aminoacyl translocation reactions.**
- **The binding site is the 50S ribosomal subunit and is identical to that of erythromycin.**

Macrolides and clindamycin share a similar mechanism of action by inhibiting bacterial protein synthesis through binding to the 50S ribosomal subunit. However, clindamycin is more effective against anaerobic bacteria.

Clindamycin

- All of them are acquired types of resistance :

Mechanisms of Resistance:

1. **Mutation in the ribosomal receptor site. (Changes in the nucleotides of the DNA, thus the AAs sequence)**
2. **Modification of the receptor by a constitutively expressed methylase (This methylase can bind to the bacterial 50S ribosomal subunit and prevent the action of clindamycin).**
3. **Enzymatic inactivation of clindamycin. (These enzymes are produced by the bacteria)**
4. **Gram positive aerobes are constitutively resistant because of poor permeability of the outer membrane.**

- **Resistance to clindamycin generally confers resistance to macrolides.**

, والعكس صحيحdespite that the antimicrobial spectra are different

There are two types of resistance:

1. <u>Acquired resistance:</u>

Happens when a microorganism that used to respond to a specific antibiotic no longer responds.

This may be due to certain changes in the microorganism.

2. <u>Constitutive resistance:</u>

Occurs when the target of the drug is not present in the microorganism being treated.

For example, penicillins and cephalosporins cannot act on bacteria that don’t have cell walls.

Clindamycin

Antibacterial spectrum:

- **Anaerobic bacteria both gram positive and gram negative, including *Bacteroides* sp.**
- ***Gardnerella spp, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina (In Bacterial Vaginosis 'BV')**
- **Many (not all) gram positive cocci (streptococci, staphylococci and pneumococci).**

It is not considered a first-line treatment for Staphylococcus . The preferred initial therapy involves anti-staphylococcal penicillins. If resistance occurs, vancomycin is typically used. In cases where vancomycin is ineffective, linezolid is considered. Clindamycin is generally reserved as a later option when linezolid also doesn't work.

- When a bacterial species is described as resistant to a specific antibiotic, this does not mean that all strains within the species are uniformly resistant. For example, although approximately 70% of Escherichia coli strains may be resistant to amoxicillin, some strains may still be susceptible. However, due to the high prevalence of resistance, amoxicillin is generally avoided in the treatment of E. coli-associated urinary tract infections. In this context, the term ‘resistance’ reflects general patterns within the species, acknowledging that strain-level variability exists. Therefore, observing that an antibiotic is effective against some strains but not others is not a contradiction, it highlights intra-species heterogeneity in antibiotic susceptibility

Clindamycin

Doctor added this slide during the lecture !

- **Clindamycin-resistant bacteria:**
- **Enterococci**
- **Aerobic gram-negative organisms**
- **GBS strains (Group B Streptococci). These cause maternal infections during pregnancy that can be transferred to the newborn.**
- **Gram-negative anaerobes such as B. fragilis. (Although Bacteroides species are generally considered susceptible to clindamycin (as mentioned in the previous slides), some strains, such as Bacteroides fragilis, may exhibit resistance. This is not a contradiction, but rather an example of strain-specific variability in antibiotic susceptibility within the same bacterial genus.)**

Clindamycin

Pharmacokinetics:

- **Widely distributed into body fluids and tissues, including bone (used to be the drug of choice for osteomyelitis) and placenta and breast milk, except brain and CSF.**
- **It penetrates well into abscesses (except for brain abscesses, not because it's ineffective, rather it's due to its inability to reach the brain. Metronidazole can be used in this case because in abscesses we have mixed bacterial infections).**
- **It is actively taken up and concentrated by phagocytic cells. (An advantage)**

Clindamycin

- **It is about 90% bound to plasma proteins. (Drug interactions may occur)**
- **It is metabolized in the liver, and both active drug and metabolite are excreted in bile and urine.**
- **t½ ~ 2.5 hours (short) in normal individuals and 6 hours in patients with anuria, but no dosage adjustment is needed in renal failure.**
- **Accumulates in severe hepatic dysfunction.**

In normal individuals, the half-life of clindamycin is about 2.5 hours. In patients with anuria, the half-life may increase to around 6 hours. This is because clindamycin is metabolized in the liver but excreted in the urine, so when urine output is absent—as in anuria—the elimination is slowed. However, the half-life does not increase dramatically.

Clindamycin

Therapeutic uses:

1. **Infections of the female genital tract (bacterial vaginosis, septic abortion and pelvic abscesses) (check next slide)**
2. **Anaerobic infections**
3. **Osteomyelitis (Clindamycin was previously used in the treatment of osteomyelitis due to its good penetration into bone tissue. However, certain fluoroquinolones are now preferred in some cases, as they also achieve therapeutic concentrations in bone)**
4. **Lung abscess**
5. **Infections resulting from fecal spillage (penetrating wounds, surgery on GIT, perforation of a viscus).**
6. **Aspiration pneumonia, in combination with an aminoglycoside or cephalosporin. (Check next slide)**

1. The pelvis, colon, and appendix are considered contaminated or non-sterile regions of the abdomen. Therefore, if these structures are accidentally ruptured during surgery or trauma, microorganisms may be released, potentially leading to infections such as intra-abdominal abscess formation.

6. In aspiration pneumonia, bacteria from the oral cavity and upper airways are introduced into the lower respiratory tract. This typically results in a mixed infection involving both anaerobic and aerobic bacteria. Clindamycin is used for its effectiveness against anaerobes. Aminoglycosides, although not active against anaerobes, are effective against certain aerobic pathogens. Cephalosporins are often added because they disrupt the bacterial cell wall, thereby enhancing the penetration and effectiveness of aminoglycosides against aerobic bacteria.

Clindamycin

The use of clindamycin can disrupt the normal microflora, predisposing patients to opportunistic infections. The most serious of these is Clostridium difficile infection, which may lead to pseudomembranous colitis and carries a mortality rate of up to 50% in severe cases.

Adverse Effects:

1. **GIT irritation: nausea, vomiting, diarrhea.**
2. **Superinfection: diarrhea & pseudomembranous colitis due to *Clostridium difficile*.**
3. **Thrombophlebitis.**
4. **Thrombocytopenia and neutropenia. (Bone marrow depression)**
5. **Allergic reactions.**

Antiherpes Agents

📌 **Another infection in the female genital system : Herpes Infection**

- Used to treat herpes simplex virus (HSV) & Varicella-zoster virus (VZV) infections.
- Include: Acyclovir,(and others)
- Is an acyclic guanosine derivative.
- It is 10 times more potent (that means that we need 1/10 of the dose only) against HSV-1 and HSV-2 than VZV (shingles).

Acyclovir

Mechanism of Action:

- **Requires 3 phosphorylation steps for activation: It is first converted to the monophosphate derivative by viral thymidine kinase (specific to viruses) and then to the di- and triphosphate by host cell enzymes.**
- **Because it requires virus enzymes first for activation, it is selectively activated, and the active metabolites accumulate in infected cells.**

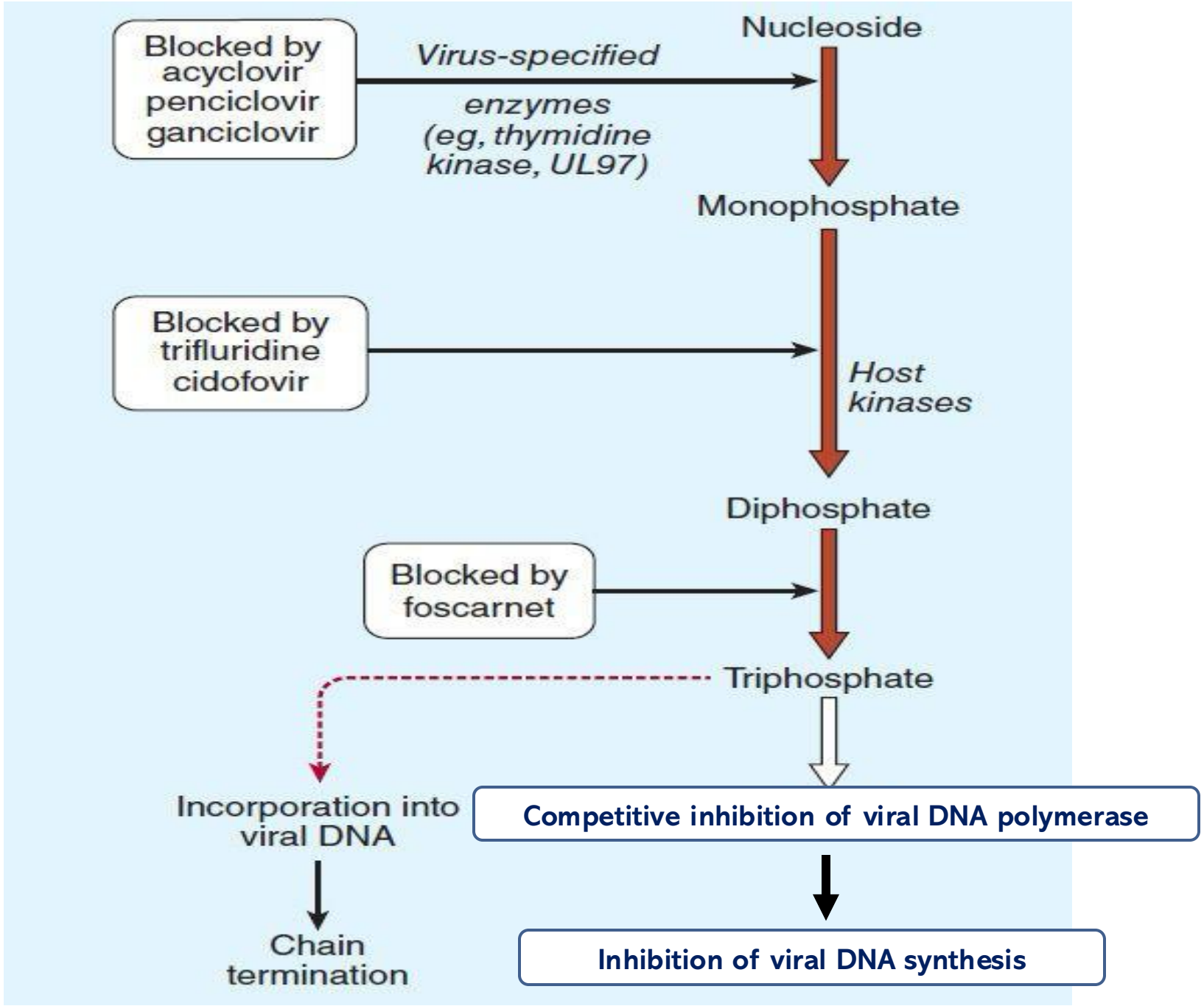
Acyclovir

- **Acyclovir triphosphate inhibits viral DNA synthesis by 2 mechanisms:**

1. **Competition with deoxy-GTP for viral DNA polymerase → binds irreversibly to DNA template.**
2. **Chain termination following incorporation into the viral DNA.**

Mechanism of resistance:

- **Due to alteration of either viral thymidine kinase or DNA polymerase.**



Mechanism of action of antiherpes agents.

Acyclovir

Bioavailability refers to the percentage of an administered drug dose that reaches the systemic circulation in an active form. In the case of acyclovir, it has low bioavailability, this means that a significant portion of the dose is lost before reaching circulation. To compensate for this low bioavailability, the administered dose is typically increased, often up to five times higher to achieve therapeutic levels.

Pharmacokinetics:

- **Bioavailability is low (15-20%), and is unaffected by food.**
- **Available in oral, intravenous, and topical formulations.**
- **Cleared primarily by glomerular filtration and tubular secretion, active transport (Both!).**
- **Half-life of elimination is ~ 3 hours in patients with normal renal function, and 20 hours in patients with anuria.**
- **Diffuses readily into most tissues and body fluids. (An advantage for treatment efficacy but a disadvantage in terms of increased adverse effects)**

Acyclovir

Therapeutic uses:

1. **Genital herpes: caused mainly by HSV-2 (although HSV-1 can also be responsible).**
2. **Herpes labialis (lip).**
3. **Herpes zoster.**
4. **Herpes encephalitis.**
5. **Neonatal herpes. (Acquired from an infected mother)**

Acyclovir

Adverse Effects:

1. **Nausea, diarrhea, headache – occasional. (These adverse effects are not mild or transient , they can be distressing to the patient, sometimes leading to reluctance to engage in daily activities)**
2. **IV administration may be associated with reversible crystalline nephropathy (drug precipitation in kidney tissues as crystals, leading to crystalluria) or interstitial nephritis (allergy in kidney); or neurologic toxicity (tremors, delirium, seizures). These are uncommon with adequate hydration and avoidance of rapid infusion rates.**

Very important!!
So, in patients with low blood volume or dehydration, **intravenous fluids** should be administered before initiating acyclovir therapy. This preventive approach is also commonly applied with several chemotherapeutic agents, where adequate hydration is essential to minimize toxicities.

- **Drug Interactions:**
- **Probenecid and cimetidine decrease acyclovir clearance and increase exposure, by inhibiting renal tubular secretion, which is one of the main pathways for acyclovir clearance. As a result, co-administration of these drugs can reduce acyclovir elimination and lead to its accumulation in the body.**

📌 **The doctor advised us to always check for drug interactions and ask patients about the medications they are taking, as multiple mechanisms of interaction may occur.**

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!