Anti-herpes Drugs

In this article, we will study in detail about various anti-herpes drugs, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be studied.

Overview of Herpes Infections

Herpes infections are very common; most adults have one or more herpes infections in their life. Herpes infections are caused by the Herpesviridae viruses, a family of DNA viruses.

Herpes Simplex Infections

Although both HSV1 and HSV2 can cause orofacial and genital infections, HSV1 more commonly causes the former and HSV2 the latter.

Important:

- HSV 1 predominantly causes infections of the labial areas (areas above the waist).
- HSV 2 predominantly causes infections in the **genital areas** (areas below the waist).

Clinical manifestations and the course of the infection depend on the patient’s age and immunological status, ranging from asymptomatic subclinical infections to life threatening in immunocompromised patients. Primary infections tend to be more severe, with systemic signs and symptoms, while repeated infections usually show isolated local involvement.

**Pathogenesis of Herpes Infections**

Mode of infection of HSV virus is through *mucosal surfaces* or through the abraded skin. Sexual infections occur in the adult (vaginal, anal, oro-genital and oro-anal transmissions). In the neonate, perinatal infection is usually contracted during passage through the birth canal. After entry into the *host*, the virus reaches the *epidermis/dermis* where *replication* starts. The virus then reaches either the *autonomic* or *sensory nerve endings*. After reaching a sufficient replication number in the nerve endings, the virus is transported *intra-axonally* into the cell bodies. 

**Centripetal motion** of the virus from the axon to the cell body and then spread to the *mucocutaneous surface* through the peripheral nerve endings is the reason for larger surface area involvement. There are occurrences of new lesions away from the *site of inoculation* and ability to recover the virus from neurons far away from the site of inoculation.

**HSV viremia** is another chief mechanism seen in HSV type 2 responsible for extension of the infection.

In the case of HSV 1, latent infection is most commonly observed in the *trigeminal ganglia*. While in the HSV 2 infection, *sacral root ganglia (s2-s5)* is most frequently affected.

**Herpes Labialis**

**Clinical Spectrum of Herpes Infections**

HSV infection is acquired as:

1. **Primary infection** (where the host acquires the infection for either type of HSV for the first time and lacks the antibodies in the serum).
2. ** Reactivation of HSV** in affected neurons (latent).

**Herpes Genitalis in Females**

When compared to a recurrent infection, the **primary infection** has a longer duration of symptoms as it involves both mucosal and extra-mucosal sites. The incubation period for both types of HSV infection is 6-8 days.

The spectrum of HSV infection includes the following conditions:

- Acute herpetic gingivostomatitis
- Acute herpetic pharyngotonsillitis
- Herpes labialis
- Genital herpes (primary, recurrent and subclinical)
- Herpetic keratitis
- Encephalitis
Varicella Zoster Infections

VZV causes chickenpox following initial exposure to the virus, and reactivation of the virus later in life causes herpes zoster (shingles).

Electron Micrograph of a Varicella (Chickenpox) Virus.


Chickenpox usually occurs in childhood and presents as a characteristic rash with a low-grade fever. In a healthy child, this infection is usually self-limiting and benign, but can be more serious in adults and immunocompromised children; in these cases, different prodromal symptoms, such as headaches, nausea, and myalgia, are possible, as well as serious clinical manifestations, leading even to death.

The structure of the virus is similar to the herpes virus with lipid envelope, icosahedral symmetry and double stranded DNA.

Herpes zoster usually occurs many years after the primary infection, manifesting as a typical vesicular rash affecting only one or two dermatomes and accompanied by pain, tingling and altered sensations or sensory loss in the affected area. A common sequela of herpes zoster is post-herpetic neuralgia (i.e., persistent pain along the distribution of the rash).

Antiviral Drugs
Acyclovir

**Mechanism of Action:**

Acyclovir is activated as follows:

1. Virus-specific enzymes (e.g., thymidine kinase) convert acyclovir to acyclovir monophosphate.
2. Host cell kinases convert acyclovir monophosphate to diphosphate and then to triphosphate.

Because virus-specific enzymes are required, acyclovir is activated only in infected cells. Some virus strains lack thymidine kinase, these viruses show resistance to acyclovir; in these cases, cross-resistance to famciclovir, ganciclovir and valacyclovir also occurs.

Acyclovir triphosphate inhibits the viral DNA synthesis via the following two mechanisms:

- It acts as a competitive substrate for DNA polymerase
- It irreversibly binds to the viral DNA and causes chain termination

**Clinical uses:** Acyclovir is used in the treatment of HSV1, HSV2 and VZV infections, even though it shows a greater potency in the treatment of HSV than VZV. The order of sensitivity is HSV1 > HSV2 > VZV = EBV. Accordingly, higher doses are required when given for VZV.

There are three formulations available: oral, intravenous and topical. Oral is unaffected by food, but bioavailability is low (20%). Topical acyclovir can be useful in skin lesions and has the advantage of no systemic reactions. In HSV encephalitis, neonatal HSV infection or other HSV and/or VZV infections in immunocompromised patients, intravenous acyclovir is a drug of choice.

**Adverse effects/toxicity:** Because the drug is activated only in infected cells, acyclovir is generally well tolerated. However, headache and gastrointestinal symptoms (nausea and diarrhea) have been observed. In some cases, intravenous administration can lead to acute renal toxicity (which is dose dependent) and some neurological adverse effects, such as seizures, delirium, etc. These adverse effects can be avoided by proper hydration of the patient during the therapy.

**Drug interactions:** Because of the possibility of renal toxicity, concurrent use with other nephrotoxic agents should be avoided. Cimetidine and probenecid increase exposure to the drug through the decreased clearance. In patients receiving concomitant zidovudine, lethargy and somnolence are possible effects.

**Contraindications:** Previous allergic reactions to acyclovir or penciclovir. Kidney disease and massive volume loss are relative contraindications because of potential kidney damage.

Valacyclovir

**Mechanism of action:** Valacyclovir is metabolized by the first pass metabolism into acyclovir. Oral valacyclovir has a much better bioavailability than oral acyclovir.

**Clinical uses:** Genital herpes, herpes labialis and VZV infections. Only oral formulation is available.
Adverse effects/toxicity: Valacyclovir has almost the same metabolism as acyclovir, making it a safe medication. In high doses, symptoms like confusion, seizures and hallucinations have been reported, but are rare. Gastrointestinal intolerance, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are possible, but extremely rare.

Contraindications: Previous allergic reactions to acyclovir or penciclovir.

Famciclovir

Mechanism of action: Famciclovir is a prodrug and is metabolized to penciclovir through first pass metabolism (deacetylation and oxidation).

Mnemonics: Fam-ous Pen

It is phosphorylated by virus-specific thymidine kinase, making this drug very specific, similar to acyclovir; it is a competitive inhibitor of DNA polymerase, but it does not cause chain termination. Penciclovir triphosphate does not have the affinity to DNA polymerase that the acyclovir triphosphate has, but it reaches a higher concentration in the cells.

Clinical uses: Genital herpes, herpes labialis and herpes zoster. Only oral formulation is available.

Adverse effects/toxicity: Headaches and gastrointestinal symptoms

Drug interactions: Famciclovir should not be administered 24 hours before to 14 days after VZV immunization.

Contraindications: Known hypersensitivity.

Penciclovir

Penciclovir is an active metabolite of famciclovir and it is available only as a topical agent. It is used in genital and labial herpes. There are no interactions and adverse effects are rare, except the application site reactions (pruritus, mild pain and transient burning) that occur in 1% of patients.

Docosanol

Docosanol inhibits the viral entry in the cells by preventing fusion between the viral envelope and the plasma membrane. It is used in the treatment of Herpes labialis and is available only as a topical agent. Application site reactions occur in 2% of patients.

Trifluridine

Mechanism of action: Trifluridine (trifluoro thymidine) inhibits DNA synthesis in HSV1, HSV2, CMV, vaccinia and several adenoviruses. Similar to other above-mentioned nucleoside analogs, it is phosphorylated intracellularly and then inhibits DNA synthesis by competitively inhibiting viral DNA polymerase. Trifluridine is not selective for infected cells, making it inadequate for systemic use.

Clinical uses: Trifluridine (topical application only) is used in the treatment of HSV1 or HSV2-associated keratoconjunctivitis and epithelial keratitis.
Cutaneous application of trifluridine, alone or in combination with interferon alfa, is effective in acyclovir-resistant HSV infections.

**Adverse effects/toxicity:** Some palpebral edema and burning sensation happens in 1-10% of patients.

**Drug interactions:** No interactions.

**Contraindications:** Previous allergic reactions.

**Ganciclovir**

**Mechanism of action:** Similar to other above-mentioned nucleoside analogs, ganciclovir is activated intracellularly by the virus-specific enzyme phosphotransferase UL97 and then inhibits DNA synthesis by competitively inhibiting viral DNA polymerase.

**Clinical uses:** Ganciclovir is mainly used in the treatment of CMV infections and it is 100 times more potent against CMV than acyclovir.

There are three formulations available: oral, intravenous and an ocular implant.

Drug administered orally has poor bioavailability, but it is less likely than IV application to cause myelosuppression.

In HIV patients, IV ganciclovir is used to delay the progression of CMV retinitis, and the effectiveness is increased when combined with foscarnet. IV administration is also recommended in immunocompromised patients suffering from CMV esophagitis, colitis and pneumonitis.

Ocular implants are used in the treatment of CMV retinitis and must be surgically replaced every 5-8 months.

**Adverse effects/toxicity:** Myelosuppression is the most common adverse effect of ganciclovir and it is usually associated with intravenous application. Adverse effects like a headache, gastrointestinal symptoms, rash and peripheral neuropathy are also observed. Very rarely, toxicity of the liver and central nervous system can be seen.

**Drug interactions:** Myelosuppression is more likely with concomitant administration of azathioprine, mycophenolate mofetil, or zidovudine. Probenecid and trimethoprim increase ganciclovir levels and ganciclovir increases dadinosine levels.

**Contraindications:** Previous allergic reactions to acyclovir or ganciclovir, severe thrombocytopenia and neutropenia.

**Valganciclovir**

Valganciclovir is metabolized to ganciclovir in the liver and intestinal wall. Only oral formulation is available and its bioavailability is better than that of ganciclovir. It is used in the treatment of CMV retinitis and as a prevention of CMV infections in transplant patients. Because valganciclovir is metabolized to ganciclovir, all the adverse effects, interactions and contraindications are the same as ganciclovir.

**Foscarnet**

**Mechanism of action:** Foscarnet (phosphonoformic acid) inhibits DNA polymerase of herpesviruses, as well as RNA polymerase and reverse transcriptase of the HIV. It does
not need to be phosphorylated in order to be active. In the aforementioned enzymes, foscarnet blocks the pyrophosphate binding site; this results in the inhibition of pyrophosphate cleavage from deoxynucleotide triphosphates. Lack of or defect in enzymes such as thymidine kinase do not confer resistance to foscarnet.

**Clinical uses:** CMV infections and acyclovir-resistant HSV and VZV infections. Because of its poor bioavailability when administered orally, only intravenous formulation is available.

**Adverse effects/toxicity:** Renal impairment and electrolyte disturbances—hypocalcemia, hypercalcemia, hypophosphatemia, hyperphosphatemia, hypokalemia and hypomagnesemia. The speed of administration has to be closely monitored and adjusted based on creatinine clearance. Genital ulcerations can occur because of the ionized drug present in the urine. Other adverse effects include gastrointestinal symptoms, liver toxicity, anemia, fatigue and central nervous system toxicity (headache, hallucinations and seizures).

**Drug interactions:** Anemia is more likely to appear in patients receiving zidovudine at the same time, while the central nervous system toxicity happens more often in patients being treated with imipenem at the same time.

**Contraindications:** Previous allergic reactions to foscarnet. The use in patients with previous renal impairment or in those receiving nephrotoxic drugs, such as amphotericin B, should be closely monitored.

**Cidofovir**

**Mechanism of action:** Cidofovir does not require viral enzymes for phosphorylation to its active diphosphate, thus making it effective against the strains of CMV and HSV without or with a defective thymidine kinase. Cidofovir is an inhibitor of viral DNA polymerase, but it also acts as its alternative substrate causing inhibition of DNA synthesis.

**Clinical uses:** Intravenous preparation is used in the treatment of CMV retinitis.

**Adverse effects/toxicity:** The most common adverse effect is proximal tubular nephrotoxicity. Each cidofovir infusion must therefore be titrated based on creatinine clearance and the presence of protein in urine, and the patient has to be hydrated during the administration of the medication. Ocular toxicity (uveitis, ocular hypotony) and neutropenia are possible.

**Drug interactions:** Concomitant administration of nephrotoxic drugs (such as amphotericin B and aminoglycosides) should be avoided. Probenecid causes increased adverse effects and drug interactions.

**Contraindications:** Known hypersensitivity. Because of the possibility of severe renal toxicity, patients with previously known renal impairment should not receive cidofovir.

**Idoxuridine**

Idoxuridine is a thymidine analog. Because it competes with thymidine, it gets inserted in the DNA, causing it to break. It is used for the treatment of HSV keratitis and genital and labial herpes. Only topical formulation (eye drops) is available. It is rarely used because acyclovir is safer and more effective.
Review Questions

1. Which of the following antiviral medications is contraindicated in patients with renal impairment?
   A. Acyclovir
   B. Penciclovir
   C. Idoxuridine
   D. Cidofovir
   E. Ganciclovir

2. Which of the following antiviral medications is known to cause severe myelosuppression?
   A. Foscarnet
   B. Idoxuridine
   C. Zidovudine
   D. Cidofovir
   E. Ganciclovir

3. Which of the following antiviral medications can be administered intravenously?
   A. Idoxuridine
   B. Valganciclovir
   C. Valacyclovir
   D. Trifluridine
   E. Acyclovir

References


Correct answers: 1D; 2E; 3E

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