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FAMILY HERPESVIRIDAE – AN OVERVIEW

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ნატო კორსანტია, ალექსანდრე კაციტაძე, ნინო ცისკარიშვილი, ნინო ადამაშვილი, თამარ გოგინაშვილი, მაკა ბიბიჩაძე, ნინო კორსანტია, თეა კაციტაძე

ჰერპესვირიდეს ოჯახი - მიმოხილვა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

რეზიუმე

ჰერპესვირუსები (ოჯახი Herpesviridae) დიდი ზომის, გარსით დაფარული ვირუსებია, რომლებსაც აქვთ ხაზოვანი ორჯაჭვიანი დნმ. დღეისათვის აღმოჩენილია ადამიანის რვა ჰერპესვირუსი, რომლებიც იყოფა სამ გვარად: ალფა-, ბეტა- და გამა-ჰერპესვირუსი. ჰერპესვირუსული ინფექციები იწვევს მნიშვნელოვან ავადობას განსაკუთრებით შიდსისა და ორგანოთა გადანერგვის მქონე პაციენტებში, დაქვეითებული იმუნური სისტემით.

თავდაპირველი ინფექციის შემდეგ, ყველა ჰერპესვირუსი რჩება ლატენტურ მასპინძელ უჯრედებში და შეიძლება შემდგომში ხელახლა გააქტიურდეს. პირველადი ინფექციით გამოწვეული კლინიკური სინდრომები შეიძლება მნიშვნელოვნად განსხვავდებოდეს ამ ვირუსების რეაქტივაციით გამოწვეული სინდრომებისგან. ჰერპესვირუსები მასპინძლის გარეთ დიდხანს არ ცოცხლობენ. ამრიგად, გადაცემა ჩვეულებრივ მოითხოვს მჭიდრო კონტაქტს. ლატენტური ინფექციის მქონე ადამიანებში ვირუსი შეიძლება ხელახლა გააქტიურდეს სიმპტომების გამოწვევის გარეშე. ასეთი პაციენტი არის უსიმპტომო, მაგრამ გადამდები.

მიუხედავად იმისა, რომ ჰერპესვირუსები გენეტიკურად და სტრუქტურულად მსგავსია, ისინი იწვევენ კლინიკური სინდრომების ფართო სპექტრს. ეპშტეინ-ბარის ვირუსმა და ადამიანის ჰერპეს ვირუსი 8-მ, ასევე ცნობილმა, როგორც კაპოშის სარკომასთან ასოცირებულმა ჰერპესვირუსმა (KSHV), შეიძლება გამოიწვიოს სხვადასხვა ფორმის სიმსივნე.

Herpesviruses (family Herpesviridae) are large, enveloped viruses that possess a linear double-strand DNA of 120–240 kb. Eight human herpesviruses were discovered, which are subdivided into three groups: alpha-, beta- and gamma-herpesvirus. Herpesvirus infections cause significant morbidity in AIDS and organ transplant patients with compromised immune systems. After initial infection, all herpesviruses remain latent within specific host cells and may subsequently reactivate. Clinical syndromes due to primary infection can vary significantly from those caused by reactivation of these viruses. Herpesviruses do not survive long outside a host; thus, transmission usually requires intimate contact. In people with latent infection, the virus can reactivate without causing symptoms; in such cases, asymptomatic shedding occurs and people can transmit infection [1].

Despite the fact that the herpesviruses are genetically and structurally similar, they cause a wide array of generally non-overlapping clinical syndromes. In contrast to other herpesviruses that are not known to cause malignancy, Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8), also known as Kaposi sarcoma–associated herpesvirus (KSHV), can cause certain cancers [2].

Both types of herpes simplex virus, **HSV-1** and **HSV-2**, can cause oral or genital infection. Most often, HSV-1 causes gingivostomatitis, herpes labialis, and herpes keratitis. HSV-2 usually causes genital lesions. Transmission of HSV results from close contact with a person who is actively shedding virus. Viral shedding occurs from lesions but can occur even when lesions are not apparent. After the initial infection, HSV remains dormant in nerve ganglia, from which it can periodically reactivate, causing symptoms. Recurrent herpetic eruptions are precipitated by overexposure to sunlight; febrile illnesses; physical or emotional stress; immunosuppression; unknown stimuli. Generally, recurrent eruptions are less severe and occur less frequently over time. Around 3.7 billion people around the world who are under the age of 50 years have HSV-1 infections [WHO, 2023].

Diseases include: Mucocutaneous infection (most common), including genital herpes, ocular infection, central nervous system (CNS) infection, neonatal herpes. HSV rarely causes fulminant hepatitis in the absence of cutaneous lesions. In patients with HIV infection, herpetic infections can be particularly severe. Progressive and persistent esophagitis, colitis, perianal ulcers, pneumonia, encephalitis, and meningitis may occur. HSV outbreaks may be followed by erythema multiforme, possibly caused by an immune reaction to the virus. Eczema herpeticum is a complication of HSV infection in which severe herpetic disease develops in skin regions with eczema.

HUMAN HERPESVIRUSES

Common Name	Other Name	Typical Manifestations
Herpes Simplex Virus Type 1	Human herpesvirus 1	Gingivostomatitis, keratoconjunctivitis, tonsillopharyngitis, herpetic whitlow, genital herpes, herpes labialis, encephalitis, viral meningitis, esophagitis, pneumonia, disseminated infection, hepatitis
Herpes Simplex Virus Type 2	Human herpesvirus 2	Oral and genital herpes, herpetic whitlow, gingivostomatitis, tonsillopharyngitis, herpes simplex keratitis, neonatal, herpes, viral meningitis, hepatitis, disseminated infection
Varicella-zoster virus	Human herpesvirus 3	Chickenpox, herpes zoster, disseminated herpes zoster
Epstein-Barr virus	Human herpesvirus 4	Infectious mononucleosis, hepatitis, encephalitis, nasopharyngeal carcinoma, Hodgkin lymphoma, Burkitt lymphoma, lymphoproliferative syndromes, oral hairy leukoplakia, gastric cancer, multiple sclerosis
Cytomegalovirus	Human herpesvirus 5	Cytomegalovirus mononucleosis, hepatitis, congenital cytomegalic inclusion disease, hepatitis, retinitis, pneumonia, colitis
Human herpesvirus 6A and 6B	-	Roseola infantum, otitis media, encephalitis
Human herpesvirus 7	-	Roseola infantum
Kaposi sarcoma-associated herpesvirus	Human herpesvirus 8	Causative role in Kaposi sarcoma and AIDS-related non-Hodgkin lymphomas, multicentric Castleman disease

Mucocutaneous herpes simplex infection. Lesions may appear anywhere on the skin or mucosa but are most frequent in the following locations: mouth or lips (perioral infection); genitals; conjunctiva and cornea. Generally, after a prodromal period (typically < 6 hours in recurrent HSV-1) of tingling, discomfort, or itching, clusters of small, tense vesicles appear on an erythematous base. Clusters vary in size from 0.5 to 1.5 cm but may coalesce. Lesions on the nose, ears, eyes, fingers, or genitals may be particularly painful.

Vesicles typically persist for a few days, then rupture and dry, forming a thin, yellowish crust. Healing generally occurs within 10 to 19 days after onset in primary infection or within 5 to 10 days in recurrent infection. Lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring. Skin lesions can develop secondary bacterial infection. In patients with depressed cell-mediated immunity due to HIV infection or other conditions, prolonged or progressive lesions may persist for weeks or longer. Localized infections can disseminate, particularly - and often dramatically - in patients who are immunocompromised.

Acute herpetic gingivostomatitis usually results from primary infection with HSV-1, typically in children. Herpetic pharyngitis can occur in adults as well as children. Through oral-genital contact, the cause can be either HSV-1 or HSV-2. Intraoral and gingival vesicles rupture, usually within several

hours to 1 or 2 days, to form ulcers. Fever and pain often occur. Difficulty eating and drinking may lead to dehydration. After resolution, the virus resides dormant in the semilunar ganglion.

Herpes labialis is usually a recurrence of HSV. It develops as ulcers (cold sores) on the vermilion border of the lip or, much less commonly, as ulcerations of the mucosa of the hard palate.

Genital herpes is a common viral sexually transmitted infection and affected > 490 million people ages 15 to 49 years old worldwide in 2023 [WHO, 2023]. Genital HSV can be caused by HSV-1 or HSV-2.

Herpes simplex keratitis, (HSV infection of the corneal epithelium) causes pain, tearing, photophobia, and corneal ulcers that often have a branching pattern.

Herpetic whitlow, a swollen, painful, erythematous lesion of the finger, results from inoculation of HSV through the skin and is most common among health care professionals.

Herpes simplex CNS infection. Herpes encephalitis occurs sporadically and may be severe. Multiple early seizures are characteristic. Viral meningitis may result from HSV-2. It is usually self-limited. Lumbosacral myeloradiculitis, typically caused by HSV-2, can occur during primary infection or reactivation of HSV-2 infection and can result in urinary retention or obstipation.

Neonatal herpes simplex develops in neonates, including those whose mothers have no suggestion of current or past herpes infection. It is most commonly transmitted during birth through contact with vaginal secretions containing HSV and usually involves HSV-2. Neonatal HSV infection usually develops between the 1st and 4th week of life, often causing mucocutaneous vesicles or central nervous system involvement. It causes major morbidity and mortality.

Diagnosis of HSV infection is often clinical based on characteristic lesions. Laboratory confirmation can be helpful, especially if infection is severe, the patient is immunocompromised or pregnant, or lesions are atypical. A Tzanck test (a superficial scraping from the base of a freshly ruptured vesicle stained with Wright-Giemsa stain) often reveals multinucleate giant cells in HSV or varicella-zoster virus infection. Definitive diagnosis is with culture, seroconversion involving the appropriate serotype (in primary infections), PCR, and antigen detection. Fluid and material for culture should be obtained from the base of a vesicle or of a freshly ulcerated lesion. HSV can sometimes be identified using direct immunofluorescence assay of scrapings of lesions. PCR of CSF and MRI are used to diagnose HSV encephalitis.

Treating primary HSV infection with medications, even if done early, does not prevent the possibility of recurrence. Isolated infections during mucocutaneous herpes simplex infection often go untreated without consequence. Acyclovir, valacyclovir, or famciclovir can be used to treat infection, especially when it is primary. Infection with acyclovir-resistant HSV is rare and occurs almost exclusively in patients who are immunocompromised. Foscarnet may be effective for acyclovir-resistant infections.

Secondary bacterial infections are treated with topical antibiotics (eg, mupirocin or neomycin-bacitracin) or, if severe, with systemic antibiotics (eg, penicillinase-resistant beta-lactams). Systemic analgesics may help. Gingivostomatitis and pharyngitis may require symptom relief with topical anesthetics (eg, dyclonine, benzocaine, viscous lidocaine; Lidocaine must not be swallowed because it anesthetizes the oropharynx, the hypopharynx, and possibly the epiglottis. Children must be watched for signs of aspiration). Severe cases can be treated with acyclovir, valacyclovir, or famciclovir.

Herpes labialis responds to oral and topical acyclovir. The duration of a recurrent eruption may be decreased by about a day by applying penciclovir 1% cream every 2 hours while awake for 4 days, beginning during the prodrome or when the first lesion appears. Toxicity appears to be minimal. Famciclovir 1500 mg as one dose or valacyclovir 2 g orally every 12 hours for 1 day can be used to treat recurrent herpes labialis. Acyclovir-resistant strains are resistant to penciclovir, famciclovir and valaciclovir.

Herpetic whitlow heals in 2 to 3 weeks without treatment. Topical acyclovir has not been shown to be effective. Oral or IV acyclovir can be used in immunosuppressed patients and those with severe infection.

Treatment of Herpes simplex keratitis involves topical antivirals, such as trifluridine, and should be supervised by an ophthalmologist. IV acyclovir should be used for therapy of Neonatal herpes simplex.

Encephalitis is treated with IV acyclovir. Treatment for 14 to 21 days is preferred to prevent potential relapse. Viral meningitis is usually treated with IV acyclovir. Acyclovir is generally very well-tolerated. However, adverse effects can include phlebitis, renal dysfunction, and, rarely, neurotoxicity (lethargy, confusion, seizures, coma; usually in the setting of renal insufficiency).

Chickenpox is caused by the **varicella-zoster virus** (human herpesvirus type 3); chickenpox is the acute invasive phase of the infection, and herpes zoster (shingles) represents reactivation of the latent phase.

Chickenpox, which is extremely contagious, is spread by Mucosal (usually nasopharyngeal) inoculation via infected airborne droplets or aerosolized particles; Direct contact with the virus (eg, via skin lesions).

Chickenpox is most communicable during the prodrome and early stages of the eruption. It is communicable from 48 hours before the first skin lesions appear until the final lesions have crusted. Indirect transmission (by carriers who are immune) does not occur. Prior to the advent of the varicella vaccine, chickenpox epidemics occurred in winter and early spring in 3- to 4-year cycles. In children who are immunocompetent, chickenpox is rarely severe. In adults and children who are immunocompromised, infection can often be serious. Mild headache, moderate fever, and malaise may occur 7 to 21 days after exposure, about 24 to 36 hours before lesions appear. This prodrome is more likely in patients > 10 years old and is usually more severe in adults. The initial rash, a macular eruption, may be accompanied by an evanescent flush. Within a few hours, lesions progress to papules and then characteristic, sometimes pathognomonic teardrop vesicles, often intensely itchy, on red bases. The lesions become pustular and then crust. Lesions evolve from macules to papules and vesicles, which then crust. A hallmark of chickenpox is that lesions develop in crops so that they are in various stages of development in any affected region. The eruption may be generalized (in severe cases) involving the trunk, extremities, and face, or more limited but almost always involves the upper trunk. Ulcerated lesions may develop on the mucous membranes, including the oropharynx and upper respiratory tract, palpebral conjunctiva, and rectal and vaginal mucosa. In the mouth, vesicles rupture immediately, are indistinguishable from those of herpetic gingivostomatitis, and often cause pain during swallowing. Scalp lesions may result in tender, enlarged suboccipital and posterior cervical lymph nodes. New lesions usually cease to appear by the 5th day, and the majority are crusted by the 6th day; most crusts disappear < 20 days after onset.

Sometimes vaccinated children develop varicella (called breakthrough varicella); in these cases, the rash is typically milder, fever is less common, and the illness is shorter; the lesions are contagious.

Secondary bacterial infection (typically streptococcal or staphylococcal) of the vesicles may occur, causing cellulitis or rarely necrotizing fasciitis or streptococcal toxic shock. Pneumonia may complicate severe chickenpox in adults, neonates, and patients of all ages who are immunocompromised, but usually not in young children who are immunocompetent. Myocarditis, hepatitis, and hemorrhagic complications may also occur. Acute postinfectious cerebellar ataxia is one of the most common neurologic complications in children; it occurs in 1/4000 cases in children younger than 15 years of age. Reye syndrome, a rare but severe childhood complication, may begin 3 to 8 days after onset of the rash, primarily following the use of aspirin. In adults, encephalitis can be life threatening [3].

Chickenpox is suspected in patients with the characteristic rash, which is usually the basis for diagnosis. The rash may be confused with that of other viral skin infections. If the diagnosis is in doubt, laboratory confirmation can be done; it requires one of the following: Polymerase chain reaction (PCR) for viral DNA; Immunofluorescent detection of viral antigen in lesions; Serologic tests; Viral culture; Tzanck smear. In serologic tests, detection of IgM antibodies to varicella-zoster virus (VZV) or

seroconversion from negative to positive for antibodies to VZV indicate acute infection. Samples are generally obtained by scraping the base of lesions and are transported to the laboratory in viral media. A Tzanck smear of a superficial scraping from the base of a freshly ruptured vesicle stained with Wright-Giemsa or toluidine blue stain demonstrates multinucleated giant cells and epithelial cells with eosinophilic intranuclear inclusion bodies in herpes simplex and herpes zoster infection. Culture can be used but has lower sensitivity than PCR and a longer turnaround time (1 to 2 weeks).

Mild cases of chickenpox in children require only symptomatic **treatment.** Relief of itching and prevention of scratching, which predisposes to secondary bacterial infection, may be difficult. Wet compresses or, for severe itching, systemic antihistamines and colloidal oatmeal baths may help. To prevent secondary bacterial infection, patients should bathe regularly and keep their underclothing and hands clean and their nails clipped. Antiseptics should not be applied unless lesions become infected; bacterial superinfection is treated with antibiotics. Patients should not return to school or work until the final lesions have crusted. Oral antivirals, when given to patients who are immunocompetent within 24 hours of the rash's onset, slightly decrease symptom duration and severity. However, because the disease is generally benign in children, antiviral treatment of healthy children ≤ 12 years old is not routinely recommended. Oral valacyclovir, famciclovir, or acyclovir should be given to healthy people at risk of moderate to severe disease, including patients with any of the following characteristics:

- ≥ 12 years old and unvaccinated (≥ 18 years old for famciclovir)
- Skin disorders (particularly eczema)
- Chronic lung disease
- Long-term salicylate therapy
- Current corticosteroid therapy
- A secondary case contracted from household contacts, because secondary cases are usually more severe than primary cases

Famciclovir or valacyclovir are the antivirals of choice for adults who are immunocompetent. Acyclovir is a less desirable choice because it has poorer oral bioavailability. Patients ≥ 1 year who are immunocompromised should be treated with IV acyclovir. Because **pregnant women** are at high risk of varicella complications, some experts recommend oral acyclovir or possibly valacyclovir for pregnant women with varicella. Although available safety data are reassuring, the safety of antiviral therapy during pregnancy is not firmly established, and there is longer experience with acyclovir in pregnancy compared to valacyclovir. Acyclovir and valacyclovir are pregnancy category B drugs. IV acyclovir is recommended for serious varicella disease in pregnant women. There are little data regarding the safety of famciclovir in pregnancy so it is not generally recommended for pregnant women [4].

Chickenpox in children is rarely severe. Severe or fatal disease is more likely in the following:

- Adults
- Patients with depressed T-cell immunity (eg, lymphoreticular cancer)
- Those receiving corticosteroids or chemotherapy or who are otherwise immunosuppressed
- Patients being treated with tumor necrosis factor (TNF) antagonists

Prevention of Chickenpox. Infection provides lifelong protection. Potentially susceptible people should take strict precautions to avoid people capable of transmitting the infection. A live-attenuated varicella vaccine is available in 2 formulations in the United States: Standard two-dose varicella vaccine and Combination measles-mumps-rubella-varicella (MMRV) vaccine. All healthy children and susceptible adults should receive 2 doses of live-attenuated varicella vaccine [5]. Vaccination is particularly important for women of child-bearing age, those at high risk for exposure, and those who have contact with individuals at higher risk for severe disease. These include healthcare professionals, teachers, child care workers, and residents and staff of nursing homes or other institutional settings (eg, correctional institutions). Serologic testing to determine immune status before vaccination in adults is usually not required. Rarely the vaccine may cause chickenpox lesions in patients who are immunocompetent, but disease is usually mild (< 10 papules or vesicles) and brief and causes few systemic symptoms. Vaccination of health care workers who do not have evidence of varicella immunity

is recommended. Susceptible health care workers who have been exposed to varicella should be vaccinated as soon as possible and kept off duty for 21 days.

Vaccination is contraindicated in

- Patients who had a severe allergic reaction (eg, anaphylaxis) after a previous dose of the vaccine or to a vaccine component
- Patients with moderate to severe acute concurrent illness (vaccination is postponed until illness resolves)
- Patients who are immunocompromised
- Pregnant women and those who intend to become pregnant within 1 month of vaccination (based on CDC recommendations) or within 3 months of vaccination (based on vaccine labeling)
- Patients taking high doses of systemic corticosteroids
- Children using salicylates

Postexposure prophylaxis. After exposure, chickenpox can be prevented or attenuated by intramuscular (IM) administration of varicella-zoster immune globulin (VariZIG). Candidates for postexposure prophylaxis include:

- People with leukemia, immunodeficiencies, or other severe debilitating illness without evidence of immunity
- Pregnant women without evidence of immunity
- Neonates whose mother developed chickenpox within 5 days before or 2 days after delivery
- Neonates born at < 28 weeks and exposed to a non-maternal source even if their mother has evidence of immunity (exposed neonates born at ≥ 28 weeks should receive immune globulin if their mother has no evidence of immunity)

The VariZIG immune globulin should be given as soon as possible (and within 10 days of exposure) and may modify or prevent varicella. Vaccination should be given as soon as possible to exposed, susceptible healthy patients eligible for vaccination (eg, age ≥ 1 year and no contraindications). Vaccination can be effective in preventing or ameliorating disease within 3 days and possibly up to 5 days after exposure.

Chickenpox and herpes zoster are caused by the varicella-zoster virus (human herpesvirus type 3); chickenpox is the acute, primary infection phase of the virus, and herpes zoster (shingles) represents reactivation of virus from the latent phase.

Herpes zoster inflames the sensory root ganglia, the skin of the associated dermatome, and sometimes the posterior and anterior horns of the gray matter, meninges, and dorsal and ventral roots. Herpes zoster frequently occurs in older adults and people living with HIV and is more frequent and severe in patients who are immunocompromised because cell-mediated immunity in these patients is decreased. There are no clear-cut precipitants. Lancinating, dysesthetic, or other pain develops in the involved site, typically followed within 2 to 3 days by a rash, usually crops of vesicles on an erythematous base. The site is usually one or more adjacent dermatomes in the thoracic or lumbar region, although a few satellite lesions may also appear. Lesions are typically unilateral and do not cross the midline of the body. The site is usually hyperesthetic, and pain may be severe. Lesions usually continue to form for about 3 to 5 days. Herpes zoster may disseminate to other regions of the skin and to visceral organs, especially in patients who are immunocompromised [6].

Geniculate zoster (Ramsay Hunt syndrome, herpes zoster oticus) results from involvement of the geniculate ganglion. Ear pain, facial paralysis, and sometimes vertigo occur. Vesicles erupt in the external auditory canal, and taste may be lost in the anterior two thirds of the tongue.

Ophthalmic herpes zoster results from involvement of the gasserian ganglion, with pain and vesicular eruption around the eye and on the forehead, in the V1 distribution of the ophthalmic division of the 5th (trigeminal) cranial nerve. Ocular disease can be severe. Vesicles on the tip of the nose (Hutchinson sign) indicate involvement of the nasociliary branch and a higher risk of severe ocular

disease. However, the eye may be involved in the absence of lesions on the tip of the nose. An ophthalmology consultation should be sought in V1 distribution zoster.

Intraoral zoster is uncommon but may produce a sharp unilateral distribution of lesions. No intraoral prodromal symptoms occur [6].

Up to 6% of patients with herpes zoster experience another outbreak, although this percentage may be higher in immunocompromised hosts. However, many patients, particularly older patients, have localized pain with variable intensity lasting > 3 months from the last crusted lesion in the involved distribution (postherpetic neuralgia). The pain of postherpetic neuralgia may be sharp and intermittent or constant and may be debilitating. It may persist for months or years or permanently.

Herpes zoster is suspected in patients with the characteristic rash and sometimes even before the rash appears if patients have typical pain in a dermatomal distribution. Diagnosis is usually based on the virtually pathognomonic rash. If the diagnosis is equivocal, detecting multinucleate giant cells with a Tzanck test can confirm infection, but the Tzanck test is positive with herpes zoster or herpes simplex. Herpes simplex virus (HSV) may cause nearly identical lesions, but unlike herpes zoster, HSV tends to recur and is not dermatomal. Viruses can be differentiated by culture or polymerase chain reaction (PCR). Antigen detection from a biopsy sample can also be used to detect herpes zoster.

Treatment with oral antivirals decreases the severity and duration of the acute eruption and decreases the rate of serious complications in patients who are immunocompromised; it may decrease the incidence of postherpetic neuralgia. In patients who are immunocompetent, antiviral therapy is often reserved for those who are ≥ 50 years in whom benefit is greatest. Treatment is also indicated in patients with severe pain, facial rash especially around the eye, and in patients who are immunocompromised. Treatment of herpes zoster should start as soon as possible, ideally during the prodrome, and is less likely to be effective if given > 72 hours after skin lesions appear, especially in the absence of newly forming lesions. Famciclovir and valacyclovir have better bioavailability with oral dosing than acyclovir, and therefore for herpes zoster, they are generally preferred. Corticosteroids do not decrease the incidence of postherpetic neuralgia. For less severely immunocompromised patients, oral famciclovir, valacyclovir, or acyclovir is a reasonable option; famciclovir and valacyclovir are preferred. For patients who are severely immuno-compromised, intravenous acyclovir is recommended. Some experts recommend treatment beyond 7 to 10 days, lasting until all lesions are crusted, for immunocompromised patients.

Although data concerning the safety of acyclovir and valacyclovir during pregnancy are reassuring, the safety of antiviral therapy during pregnancy is not firmly established. Because congenital varicella can result from maternal varicella but rarely results from maternal zoster, the potential benefit of treatment of pregnant patients should outweigh possible risks to the fetus. Pregnant patients with severe rash, severe pain, or ophthalmic zoster can be treated, preferably with acyclovir, because there is longer experience with its use in pregnancy as compared to other medications, although valacyclovir remains an option. There are little data regarding the safety of famciclovir in pregnancy, so it is not generally recommended in pregnant women. Management of postherpetic neuralgia can be particularly difficult. Treatments include gabapentin, pregabalin, cyclic antidepressants, topical capsaicin or lidocaine ointment, and botulinum toxin injection. Opioid analgesics may be necessary. Intrathecal methylprednisolone may be of benefit. A recombinant zoster vaccine is recommended for adults ≥ 50 years whether they have had herpes zoster or been given the older, live-attenuated vaccine or not; 2 doses of the recombinant zoster vaccine are given 2 to 6 months apart [7]. The recombinant zoster vaccine is also recommended for adults ≥ 19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy, including those with a prior history of varicella, varicella vaccine, or herpes zoster [8,10].

A post marketing observational study observed an increased risk of Guillain-Barre syndrome during the 42 days following vaccination with the recombinant zoster vaccine, and as a result some clinicians avoid recombinant zoster vaccine in patients with a prior history of Guillain-Barre syndrome [9].

Infectious mononucleosis is caused by **Epstein-Barr virus** (EBV, human herpesvirus type 4) and is characterized by fatigue, fever, pharyngitis, and lymphadenopathy. Fatigue may persist weeks or months. Severe complications, including airway obstruction, splenic rupture, and neurologic syndromes, occasionally occur. Diagnosis is clinical or with EBV serologic testing. Treatment is supportive.

EBV is a herpesvirus that infects 50% of children before age 5. Over 90% of adults are seropositive for EBV. Its host is humans. EBV infection is usually asymptomatic [1,11]. After exposure in the oral cavity, EBV infects B lymphocytes. Morphologically abnormal (atypical) lymphocytes develop, mainly from CD8+ T cells that respond to the infection. After primary infection, EBV remains within the host, primarily in B lymphocytes, for life and undergoes intermittent asymptomatic shedding from the oropharynx. The virus is detectable in oropharyngeal secretions of 10 to 20% of healthy EBV-seropositive adults. Shedding increases in frequency and titer in patients who are immunocompromised (eg, organ allograft recipients, people living with HIV). EBV has not been recovered from environmental sources and is not very contagious.

Transmission may occur via transfusion of blood products but much more frequently occurs via kissing between an uninfected and an EBV-seropositive person who is shedding the virus asymptomatically. Only about 5% of patients acquire EBV from someone who has acute infection. Early childhood transmission occurs more frequently among lower socioeconomic groups and in crowded conditions.

EBV is statistically associated with and likely has a causal role in Burkitt lymphoma, Certain B-cell tumors in patients who are immunocompromised, Certain forms of Hodgkin lymphoma, Nasopharyngeal carcinoma, Certain gastric cancers, Multiple sclerosis. EBV does not cause chronic fatigue syndrome. However, it rarely causes a syndrome that may include fever, interstitial pneumonitis, pancytopenia, hepatitis, or uveitis (ie, chronic active EBV) [11,20].

In most young children, primary EBV infection is asymptomatic. Symptoms of infectious mononucleosis develop most often in older children and adults. The incubation period is about 30 to 50 days. Fatigue can last for months but is usually maximal during the first 2 to 3 weeks. Most patients have the triad of Fever, Pharyngitis and Adenopathy. Fever usually peaks in the afternoon or early evening, with a temperature around 39.5° C, although it may reach 40.5° C. Pharyngitis may be severe, painful, and exudative and may resemble streptococcal pharyngitis. Adenopathy is usually symmetric and may involve any group of nodes, particularly the anterior and posterior cervical chains. Adenopathy may be the only manifestation. Other symptoms and signs include: Splenomegaly; Mild hepatomegaly and hepatic percussion tenderness; Periorbital edema and palatal petechiae; Less frequently maculopapular eruptions; Rarely jaundice. Splenomegaly, which occurs in about 50% of cases [1] is maximal during the 2nd and 3rd week and usually results in only a barely palpable splenic tip. Although recovery is usually complete, complications may be dramatic.

Neurologic complications are rare but may include encephalitis, seizures, Guillain-Barre syndrome, peripheral neuropathy, viral meningitis, myelitis, cranial nerve palsies, and psychosis. Encephalitis may manifest with cerebellar dysfunction, or it may be global and rapidly progressive, similar to herpes simplex encephalitis, but is usually self-limited.

Hematologic complications are usually self-limited. They include Granulocytopenia, Thrombocytopenia and Hemolytic anemia. Transient mild granulocytopenia or thrombocytopenia occurs in about 50% of patients; severe cases with bacterial infection or bleeding occur less frequently. Hemolytic anemia is often due to anti-i-specific cold-agglutinin antibodies.

Splenic rupture can have severe consequences. It can result from splenic enlargement and capsular swelling, which are maximal 10 to 21 days after presentation. A history of trauma is present only about half of the time. Rupture is usually painful but occasionally causes painless hypotension.

Respiratory complications include, rarely, upper airway obstruction due to pharyngeal or paratracheal lymphadenopathy; respiratory complications may respond rapidly to corticosteroids.

Hepatic complications include elevated aminotransferase levels (about 2 to 3 times normal, returning to baseline over 3 to 4 weeks); they occur in about 90% of patients [1]. If jaundice or more severe enzyme elevations occur, other causes of hepatitis should be investigated [11].

Infectious mononucleosis should be suspected in patients with typical symptoms and signs. Exudative pharyngitis, anterior cervical lymphadenopathy, and fever may be clinically indistinguishable from those caused by group A beta-hemolytic streptococci. However, posterior cervical or generalized adenopathy or hepatosplenomegaly suggests infectious mononucleosis. Moreover, detection of streptococci in the oropharynx does not exclude infectious mononucleosis. Primary HIV infection can produce a clinical picture resembling acute EBV infection.

HIV enzyme-linked immunosorbent assay (ELISA)/Western blot is usually negative during the acute infection and thus should not be used alone to diagnose early primary HIV infection. Quantitative HIV RNA and p24 antigen detection are more sensitive for diagnosing acute HIV infection because HIV RNA and p24 antigen are present in blood before HIV antibodies develop.

Cytomegalovirus (CMV) may also cause a mononucleosis syndrome, with atypical lymphocytosis as well as hepatosplenomegaly and hepatitis but usually not with severe pharyngitis. Toxoplasmosis may cause a syndrome similar to infectious mononucleosis with fever and lymphadenopathy but usually not with pharyngitis.

Laboratory diagnosis usually involves a complete blood count and EBV serologic testing. Lymphocytes that are morphologically atypical account for up to 30% of the white blood cells. Although individual lymphocytes may resemble leukemic lymphocytes, lymphocytes are heterogeneous, which is unlikely in leukemia. Atypical lymphocytes may also be present in HIV or CMV infection, hepatitis B, influenza B, rubella or other viral illnesses, so diagnosis requires serologic testing. However, very high atypical lymphocyte counts are typically seen only in primary EBV and CMV infection.

Two serologic tests are used to diagnose acute EBV infection:

- Heterophile antibody testing
- Specific EBV antibody testing

Heterophile antibodies are measured using various agglutination card (monospot) tests. However, heterophile antibodies are present in only 50% of patients < 5 years and in about 80 to 90% of adolescents and adults with infectious mononucleosis. Importantly, the heterophile antibody test may be false-positive in some patients with acute HIV infection. The titer and prevalence of heterophile antibodies rise during the 2nd and 3rd week of illness. Thus, if the diagnosis is suspected and the heterophile antibody test is negative early in clinical illness (in the first week), testing can be repeated approximately 7 days later. Due to the potential for false positive or negative results, the Centers for Disease Control and Prevention (CDC) does not recommend heterophile antibodies to diagnose primary EBV infection. However, a positive heterophile antibody test in the appropriate clinical situation is generally sufficient to confirm the diagnosis of primary EBV. Alternatively, EBV antibody testing can be performed.

EBV-specific antibody testing is highly sensitive. The presence of IgM antibodies to the EBV viral capsid antigen (VCA) indicates primary EBV infection (these antibodies disappear within 3 months after infection). IgG VCA (EBV VCA-IgG) also develops early in primary EBV infection, but these antibodies persist for life. EBV nuclear antigen (EBNA-IgG) antibodies develop later (after 2 to 4 months) in acute EBV infection and also persist for life. If EBV antibody titers are negative or indicate remote infection (ie, positive for IgG antibodies and negative for IgM antibodies), other diagnoses that can present with similar symptoms should be considered.

Treatment of infectious mononucleosis is supportive. Patients are encouraged to rest during the acute phase but can resume activity when fever, pharyngitis, and malaise abate. To prevent splenic rupture, patients should avoid heavy lifting and contact sports for 1 month after presentation and until splenomegaly (which can be monitored by ultrasonography) resolves. Although corticosteroids hasten defervescence and relieve pharyngitis, they generally should not be used in uncomplicated disease. Corticosteroids can be helpful for complications such as impending airway obstruction, severe thrombocytopenia, and hemolytic anemia. Although oral or IV acyclovir decreases oropharyngeal

shedding of EBV, there is no convincing evidence to warrant its clinical use in EBV mononucleosis. Infectious mononucleosis is usually self-limited. Duration of illness varies; the acute phase lasts about 2 weeks. Generally, 20% of patients can return to school or work within 1 week, and 50% within 2 weeks. Fatigue may persist for several more weeks or, in up to 10% of cases, for months. Death occurs in < 1%, mostly resulting from complications (eg, encephalitis, splenic rupture, airway obstruction).

Cytomegalovirus (CMV, human herpesvirus type 5) can cause infections that have a wide range of severity. A syndrome of infectious mononucleosis that lacks severe pharyngitis is common. Severe focal disease, including retinitis, can develop in HIV-infected patients and in organ transplant recipients and other patients who are immunocompromised. Severe systemic disease can develop in neonates and patients who are immunocompromised. Laboratory diagnosis, helpful for severe disease, may involve culture, serologic testing, biopsy, or antigen or nucleic acid detection. Ganciclovir and other antiviral medications are used to treat severe disease, particularly retinitis [2,12].

CMV (human herpesvirus type 5) is transmitted through blood, body fluids, or transplanted organs. Infection may be acquired transplacentally or during birth. Prevalence increases with age; 50 to 90% of adults have CMV infection (resulting in lifelong latent infection) [2]. Lower socioeconomic groups tend to have a higher prevalence. Congenital CMV infection may be asymptomatic or may cause abortion, stillbirth, or postnatal death. Complications include extensive hepatic and central nervous system (CNS) damage. Acquired infections are often asymptomatic. An acute febrile illness, termed CMV mononucleosis, may cause hepatitis with elevated aminotransferases (usually subclinical without jaundice), and atypical lymphocytosis similar to infectious mononucleosis due to Epstein-Barr virus (EBV).

Postperfusion/posttransfusion syndrome can develop 2 to 4 weeks after transfusion with blood products containing CMV. It causes fever lasting 2 to 3 weeks and the same manifestations as CMV mononucleosis. In **patients who are immunocompromised,** CMV is a major cause of morbidity and mortality. Disease often results from reactivation of latent virus. The lungs, gastrointestinal tract, or CNS may be involved. In the terminal phase of AIDS, CMV infection causes retinitis about 30% of patients and causes funduscopically visible retinal abnormalities. Ulcerative disease of the colon (with abdominal pain and gastrointestinal bleeding) or of the esophagus (with odynophagia) may occur [13,14].

Diagnosis of Cytomegalovirus:

- Detection of CMV antigen or DNA
- Urine culture in infants
- Biopsy of tissue that may be infected in patients who are immunocompromised
- Serologic testing

CMV infection is suspected in

- Healthy people with mononucleosis-like syndromes
- Patients who are immunocompromised and have gastrointestinal, lung, CNS, or retinal symptoms
- Neonates with systemic disease

CMV mononucleosis can be differentiated from infectious (EBV) mononucleosis by the usual lack of pharyngitis, a negative heterophile antibody test, and positive CMV serologic testing. CMV infection affecting the liver can be differentiated from other viral hepatitis infections by hepatitis serologic testing Laboratory confirmation of primary CMV infection is necessary only to differentiate it from other, particularly treatable, conditions or serious disease, such as primary HIV.

Seroconversion can be demonstrated by development of CMV antibodies and indicates new CMV infection. However, CMV disease can also result from reactivation of latent disease in immunocompromised hosts. Reactivation of CMV can result in virus in the urine, other body fluids, or tissues, but the presence of CMV in body fluids and tissues does not always indicate disease and may merely represent viral shedding. Therefore, biopsy showing CMV-induced abnormalities in infected tissue is often necessary to demonstrate invasive disease. Quantitative detection of CMV antigen or DNA in the peripheral blood can also be very helpful because an elevated or rising CMV viral load is often

highly suggestive of invasive disease. Such CMV detection can be particularly helpful in patients who are severely immunocompromised with compatible clinical syndromes in whom biopsy may not be feasible. Diagnosis of CMV infection in infants can be made by urine culture.

Treatment of Cytomegalovirus. For serious disease antivirals (eg. ganciclovir, valganciclovir, foscarnet, cidofovir, maribavir) are used. CMV retinitis, which occurs mostly in AIDS patients, is treated with systemic antivirals. Anti-CMV medications are used to treat severe disease other than retinitis but are less consistently effective than in retinitis. Most patients receive induction therapy with IV ganciclovir or oral valganciclovir. Maintenance (suppressive) therapy with ganciclovir or valganciclovir is given after induction. Alternatively, IV foscarnet can be given with or without ganciclovir. Adverse effects of IV foscarnet are significant and include nephrotoxicity, symptomatic hypocalcemia, hypomagnesemia, hyperphosphatemia, hypokalemia, and CNS effects. Combination therapy with ganciclovir and foscarnet increases efficacy as well as adverse effects. Cidofovir therapy is another alternative. Efficacy of cidofovir is similar to that of ganciclovir or foscarnet. Significant adverse effects, including renal failure, limit its use. Cidofovir may cause iritis or ocular hypotony (intraocular pressure ≤ 5 mm Hg). The potential for nephrotoxicity can be reduced by giving probenecid and prehydration with each dose. However, the adverse effects of probenecid, including rash, headache, and fever, may be significant enough to prevent its use. Maribavir is an oral medication for treatment of refractory CMV disease. Maribavir has a novel mechanism of action, targeting the viral UL97 kinase, and prevents viral maturation. It is active against CMV that is resistant to ganciclovir. Maribavir cannot be coadministered with ganciclovir or valganciclovir.

With any of the maintenance regimens, clinicians can consider stopping maintenance therapy after 3 months of CMV therapy in HIV-infected patients who are taking antiretroviral therapy (ART) and have had a CD4 count of ≥ 100 cells/mL for 3 months. Intravitreal antiviral therapy should be used in combination with systemic therapy for patients with CMV retinitis that immediately threatens sight (ie, disease involving or close to the optic nerve or macula). Even patients receiving ocular injections need systemic therapy to prevent CMV in the contralateral eye and extraocular tissues.

Prophylaxis or preemptive treatment (actively monitoring patients by viral load and giving antivirals to those with evidence of infection) is effective for preventing CMV disease in solid organ or hematopoietic cell transplant recipients infected with CMV and at risk of CMV disease. Medications used include ganciclovir, valganciclovir, and foscarnet. Letermovir is a newer agent with a novel mechanism of action that can be used for prophylaxis in bone marrow or renal transplantation. It has many important drug interactions, including with cyclosporine, tacrolimus, sirolimus, and voriconazole.

Three recently discovered members of the human herpesvirus (HHV) family are **HHV-6, HHV-7**, and **HHV-8**. The closely homologous HHV-6 and HHV-7 are ubiquitous, with nearly universal prevalence in persons older than 6 years. Human herpesvirus 8 partly shares the predilection of its 2 siblings for latency in lymphoid tissues but has a more variable demographic distribution. All 3 HHVs are actively investigated for their role in multiple pathologic abnormalities and have important cutaneous manifestations. Dermatologists typically encounter HHV-6 and HHV-7 in classic roseola infantum, whereas HHV-8 is also known as Kaposi sarcoma (KS)–associated herpesvirus. However, new disease associations, novel diagnostic evaluations, and developments in antiviral therapies herald the possibility of new advances in the diagnosis and treatment of HHV-6, HHV-7, and HHV-8 [15].

Human herpesvirus 6 has 2 variants, A and B, although new evidence suggests that these subtypes are distinct viruses, each with its own strains. Human herpesvirus 6A has been found more commonly in skin biopsy specimens from immunocompromised patients and is considered a possible cofactor in AIDS progression. In comparison, HHV-6B is thought to be the primary etiologic agent in roseola. The cellular receptor for HHV-6 is CD46, which is expressed on all nucleated cells. It accounts for the wider tropism of HHV-6 compared with that of HHV-7, which uses CD4, the marker of a T-lymphocyte subclass. An estimated 80% to 90% of the population sheds HHV-6 and HHV-7 intermittently in saliva. Human herpesvirus 6 can also integrate into the human chromosome as an ingenious means of achieving latency and vertical transmission. A recent chromosomal analysis confirmed that HHV-6 can be present in every

cell of congenitally infected children. Such congenital presence of the virus is a confounding factor in epidemiologic and diagnostic studies. Clinically, the mode of transmission for HHV-6 and HHV-7 is probably less relevant because their ubiquity and nearly universal childhood serum positivity suggest that exposure prevention is unlikely to be an option for controlling the spread of HHV-6 and HHV-7.

Similar to HHV-8, HHV-6 and HHV-7 may also have oncogenic properties. Although no cutaneous malignancy has been clearly linked to any beta Herpesviridae, neoplastic transformation of human epidermal keratinocytes has been shown in vitro. The integration of HHV-6 into telomeres with subsequent viral-induced telomere elongation could account for part of its oncogenic properties and part of its ability to evade the human immune system.

HHV-8, Human herpesvirus 8 is a member of the gamma Herpesviridae subfamily and a member of the Rhadinovirus genus. It has multiple distinct subtypes and, similar to HHV-6 and HHV-7, a predilection for lymphoid tissue. Longitudinal detection difficulties preclude establishment of HHV-8 prevalence, which is thought to approximately mirror that of KS, with relatively low rates in the United States, except where KS is endemic and high rates exist. However, the prevalence of HHV-8 does not completely correlate with KS prevalence because there are subpopulations with high HHV-8 seropositivity and nearly unknown KS. In the United States, the seroprevalence of HHV-8 is usually estimated to be less than 10%, whereas estimates of the prevalence of KS usually fall below 0.1%. Human herpesvirus 8 has been found in seminal fluid, nasal secretions, and saliva, but its mode of transmission remains enigmatic. Seropositivity is unusual in infancy, which argues against widespread vertical transmission. Kaposi sarcoma is more common in homosexual than heterosexual persons with AIDS. The high prevalence in prepubertal children in endemic areas suggests that sexual transmission is unlikely to be the sole mode of infection. A study of HHV-8–seropositive men who had sex with men and no clinical evidence of KS showed that exposure to infectious saliva is a risk factor for HHV-8 acquisition. However, this association alone does not explain the prevalence of disparities between homosexual and heterosexual populations. Other likely routes of transmission are the transplant of infected organs, transfusion of unprocessed blood, and shared use of injection needles.

Cutaneous Disease Caused by HHV-6 and HHV-7. The identified disease association of HHV-6 and HHV-7 is roseola infantum, also known as exanthem subitum, which develops in only a few infected children. On the basis of isolation of the virus and seroconversion in blood samples from 4 patients in the febrile phase of the illness, Yamanishi et al. proposed a causal association in 1988. One year later, a report from a prospective study of 38 children confirmed HHV-6 viremia in 100% of patients with roseola infantum in the early stages of the disease. More recently, roseola and the cutaneous eruptions associated with primary HHV-6 infection have been connected to a specific type of viral encephalopathy. A more debated association of the 2 viruses is pityriasis rosea. Studies linking HHV-6 and HHV-7 with pityriasis have involved tissue, whole blood, and serum analysis. Temporal case clustering from different world regions using regression analysis supported a pattern of seasonal cases compatible with an infectious etiology. Although some studies showed a clear association with HHV-6 and HHV-7, others found HHV-6 and HHV-7 to occur more commonly in controls than in persons with pityriasis. However, not all studies can be taken at face value. Given the nearly universal prevalence of HHV-6 and HHV-7, checking for viral DNA alone, without testing for an altered antibody response to show active infection, is insufficient to establish or disprove an association.

Human herpesvirus 7, but not HHV-6, is currently also a candidate for the etiology of lichen planus. In skin biopsy specimens from 33 patients, cells infected by HHV-7 were identified more frequently in lichen planus lesions than in skin without lesions or in psoriatic or healthy skin. Moreover, clinical remission after treatment was associated with a decrease in HHV-7 viral DNA. In addition, multiple case reports link HHV-6 and HHV-7 to other cutaneous disorders, including HHV-6 in Stevens-Johnson syndrome, thrombocytopenic purpura, purpura fulminans, papular-purpuric gloves and socks syndrome, and Gianotti Crosti syndrome. Human herpesvirus 6 and HHV-7 may also contribute to other disease processes with dermatologic implications, such as drug reactions and transplant complications [19].

Herpesviridae are strong candidates in the quest to better understand the pathogenesis of drug-induced hypersensitivity syndrome (DIHS), particularly drug reaction with eosinophilia and systemic

symptoms (DRESS). Data from 40 patients with DRESS suggest that it is a consequence of activated immune cells directed against herpesvirus antigens. Seventy-six percent of these patients showed reactivation of Epstein-Barr virus, HHV-6, or HHV-7. This reactivation, in turn, led to oligoclonal proliferation of activated CD8 T lymphocytes directed against viral antigens and to the inappropriate attack of host visceral and cutaneous tissue. Thus, the viral involvement in DRESS may result partly from drug-induced HHV reactivation. In addition, the pathogenesis can be enhanced by the combined modulation of inflammatory cytokines produced by the interplay of the suspected drug and the virus. Traditionally, clinically significant reactivation of HHV-6 has been detected only after DIHS onset [16].

TABLE. Cutaneous Disease Associations of HHV-6, HHV-7, and HHV-8

HHV-6	Roseola infantum HHV-6 encephalopathy (with cluster of convulsions in eruptive stage) Pityriasis rosea Lichen planus Scleroderma Gianotti-Crosti syndrome DIHS/DRESS Stevens-Johnson syndrome Gloves and socks syndrome Thrombocytopenic purpura/purpura fulminans Graft-vs-host disease
HHV-7	Roseola infantum Pityriasis rosea Lichen planus DIHS/DRESS Graft-vs-host disease
HHV-8	Kaposi sarcoma Exanthem with primary infection

The diagnosis and management of HHV-6 and HHV-7 by cutaneous manifestations usually depend on clinical acumen rather than viral detection. Each disease might also have unique nonviral features. However, discerning the presence of HHV-6 and HHV-7, if not necessarily their contribution to skin abnormalities, has become increasingly sophisticated and may play an increasing role in the future. Similarly, the presence of HHV-8 is helpful in diagnosing KS, particularly when there are early lesions that are easily confused with bruises or other vascular tumors.

Viral diagnostic techniques can be divided broadly into DNA/RNA detection, antigen assays, and antibody assays. Generally, the probability of viral detection can be amplified by culture, but the procedure is typically too time-consuming to have clinical utility. Skin biopsy specimens are tested by antigen assays, polymerase chain reaction, or, if available, electron microscopy. When applied to tissue, polymerase chain reaction, particularly real time techniques, is highly sensitive and facilitates discrimination even of viral subtypes such as HHV-6A and HHV-6B. However, on the one hand, viral DNA may still be below the detection limits in biopsied tissues, and, on the other hand, the mere detection of viral nucleic acid does not prove its contribution to pathologic abnormalities. When applied to serum, nucleic acid amplification techniques tend to be less sensitive than do HHV-specific antibodies and may result in false-positives from contamination, particularly in persons with congenital HHV [17].

No antiviral agent or immunotherapy has been specifically licensed to treat or prevent HHV-6A and -6B-associated diseases. While ganciclovir and foscarnet have antiviral activity against HHV-6B, as yet there is insufficient evidence of their value in pre-emptive or prophylactic treatment against HHV-6B-related encephalitis in patients with HCT. Oral brincidofovir has in vitro activity against both HHV-6B and HCMV and was evaluated in a randomized trial to test its efficacy in preventing complications from HCMV reactivation. Stored sera from the study allowed an assessment of its ability to prevent HHV-6B viremia, as well. Oral brincidofovir reduced the cumulative incidence of HHV-6B viremia at high risk, but not low risk, patients. The study was too small to assess its ability to prevent HHV-6B-related encephalitis.

Promising in vitro efficacy of several newer anti-herpesvirus drugs was reported—nucleoside analogs, nucleotide analogs, prodrugs (such as brincidofovir), drugs directed as the helicase/primase complex and various protein-protein interactions, and inhibitors of protein kinase and of DNA cleavage and packaging. Other new drugs target cellular proteins essential for viral replication (eg, inhibitors of cyclin-dependent kinases and the proteasome). Finally, several drugs approved for other purposes have been found to have activity against HHV-6A and -6B - eg, leflunomide, artesunate, sirolimus, and everolimus [18].

Humans and herpesviruses (HSV) have probably been linked for thousands of years. In recent decades, research has explored many aspects of herpes virus infections, from severe infections to mild or

subclinical manifestations. There are several conditions that are associated with herpes virus reactivation, ranging from immune-regulatory modifications in the elderly to transplant-related complications.

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FAMILY HERPESVIRIDAE – AN OVERVIEW

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SUMMARY

Herpesviruses (family Herpesviridae) are large, enveloped viruses that possess a linear double-strand DNA of 120–240 kb. Eight human herpesviruses were discovered, which are subdivided into three genera: alpha-, beta- and gamma-herpesvirus. Herpesvirus infections cause significant morbidity in AIDS and organ transplant patients with compromised immune systems.

After initial infection, all herpesviruses remain latent within specific host cells and may subsequently reactivate. Clinical syndromes due to primary infection can vary significantly from those caused by reactivation of these viruses. Herpesviruses do not survive long outside a host; thus, transmission usually requires intimate contact. In people with latent infection, the virus can reactivate without causing symptoms; in such cases, asymptomatic shedding occurs and people can transmit infection.

Despite the fact that the herpesviruses are genetically and structurally similar, they cause a wide array of generally non-overlapping clinical syndromes.

In contrast to other herpesviruses that are not known to cause malignancy, Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8), also known as Kaposi sarcoma–associated herpesvirus (KSHV), can cause certain cancers.

Keywords: Herpes, Herpesviridae, chickenpox, Epstein-Barr, Kaposi sarcoma