



Medical Virology for 2nd Year M.D. Students

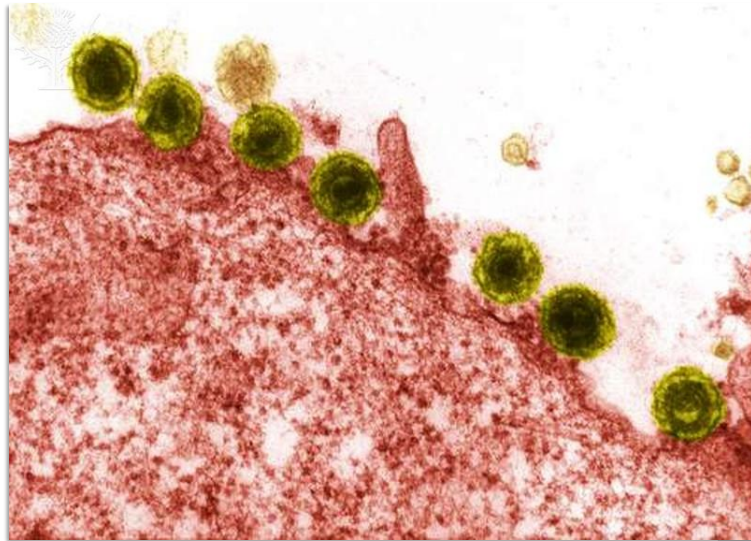


Herpesviridae

University of Jordan
School of Medicine
Section of Microbiology & Immunology
Malik Sallam, M.D., Ph.D.

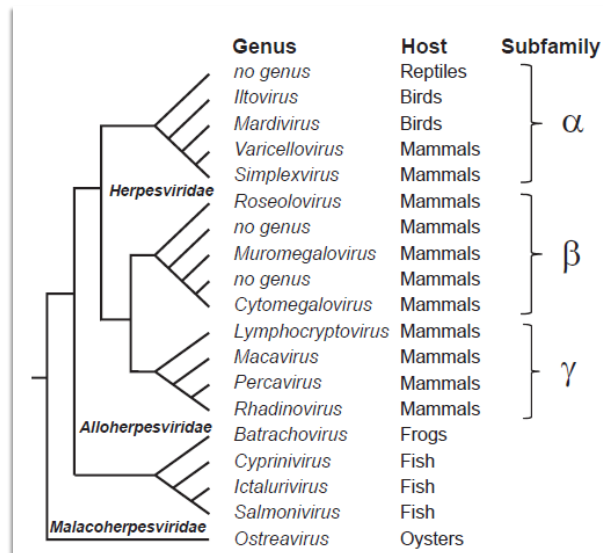


How to be a member of Herpesviridae?





Taxonomy/Classification of Herpesvirales





Taxonomy/Classification of human Herpesviridae



<i>Human HV 1</i>	HHV-1	Herpes simplex virus [type] 1	α S	152
<i>Human HV 2</i>	HHV-2	Herpes simplex virus [type] 2	α S	155
<i>Human HV 3</i>	HHV-3	Varicella-zoster virus	α V	125
<i>Human HV 4</i>	HHV-4	Epstein-Barr virus	γ L	172
<i>Human HV 5</i>	HHV-5	Cytomegalovirus (CMV)	β C	236
<i>Human HV6A</i>	HHV-6A	HHV-6 variant A	β R	159/170
<i>Human HV6B</i>	HHV-6B	HHV-6 variant B	β R	162/168
<i>Human HV 7</i>	HHV-7		β R	145
<i>Human HV 8</i>	HHV-8	Kaposi's sarcoma– associated HV (KSHV)	γ R	170/210



Important properties of Herpesviruses



Virion: Spherical, 150–200 nm in diameter (icosahedral)

Genome: Double-stranded DNA, linear, 125–240 kbp, reiterated sequences

Proteins: More than 35 proteins in virion

Envelope: Contains viral glycoproteins, Fc receptors

Replication: Nucleus, bud from nuclear membrane

Outstanding characteristics:

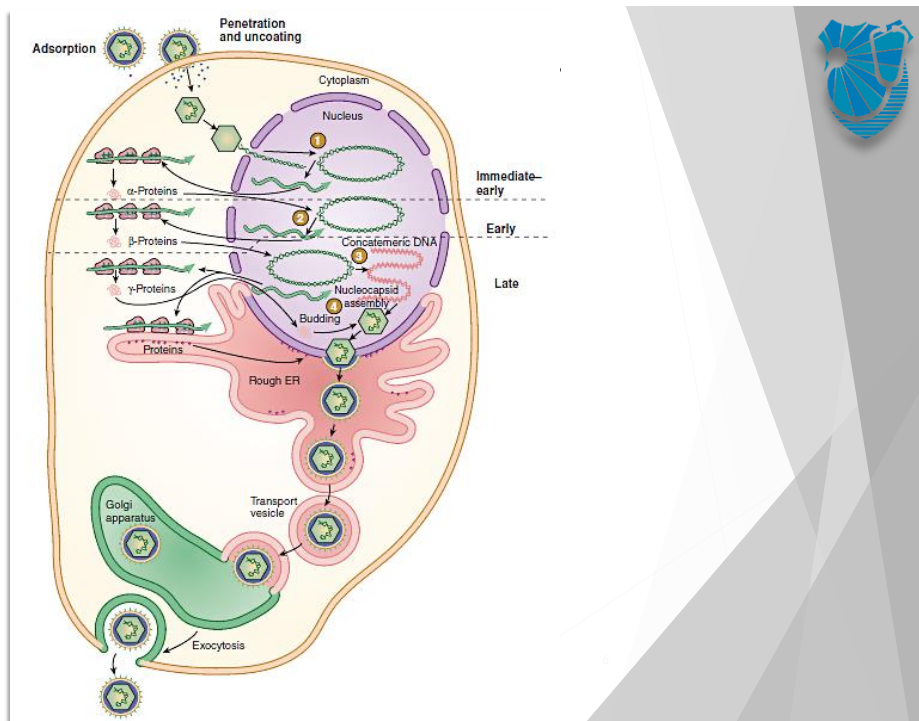
Encode many enzymes

Establish latent infections

Persist indefinitely in infected hosts

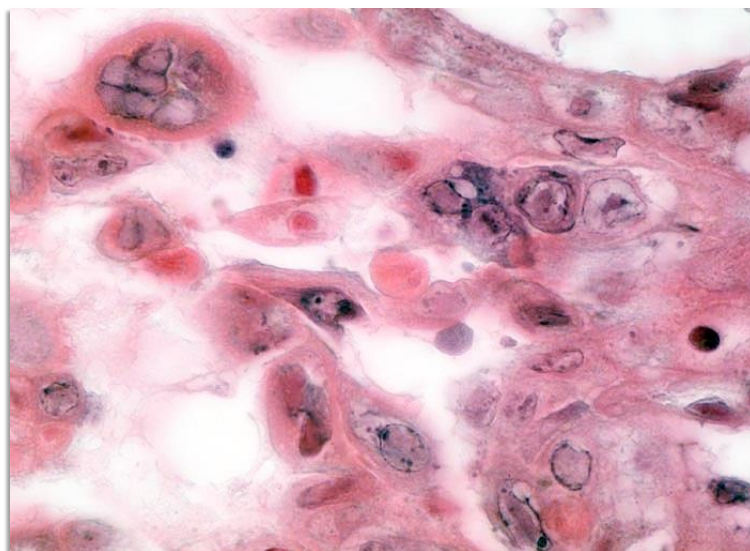
Frequently reactivated in immunosuppressed hosts

Some cause cancer



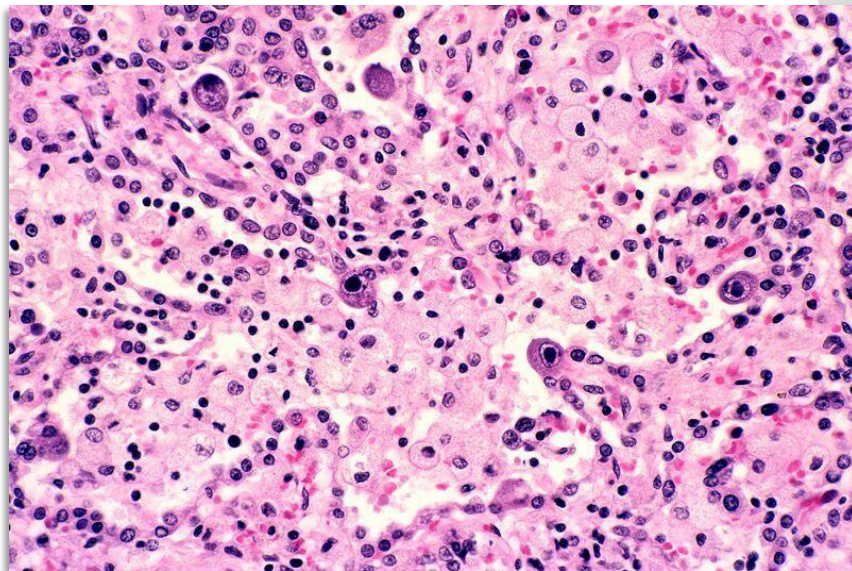


Herpesviridae CPE





Herpesviridae CPE





Herpes simplex virus





Herpes simplex virus





Herpes simplex virus





Herpes simplex virus





Herpes simplex virus transmission





Herpes simplex viruses



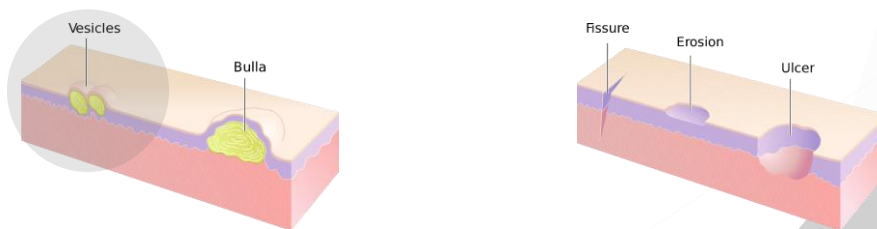
- HSVs cause cytolytic infections.
- Pathologic changes are due to:
 - (1) Necrosis of infected cells.
 - (2) The inflammatory response.
- Lesions in the skin and mucous membranes are similar for HHV-1 and HHV-2.
- Pathologic changes are similar for primary and recurrent infections but vary in degree, reflecting **the extent of viral cytopathology**.



Herpes simplex viruses characteristic lesion



Vesicles are circumscribed epidermal elevations containing clear fluid and less than 1 cm in diameter. If the lesion has a diameter of greater than 1 cm, it is called a **bulla**. Vesicles and bullae are commonly called **blisters**.





Herpes simplex viruses



▪ **Primary infection**

- Viral replication occurs first at the site of infection.
- HSV then invades local nerve endings and is transported by retrograde axonal flow to dorsal root ganglia.
- After further replication, latency is established.
- Oropharyngeal infections result in latent infections in the **trigeminal ganglia**.
- Genital infections lead to latently infected **sacral ganglia**.



Herpes simplex viruses



- **Latent infection**

- Virus resides in latently infected ganglia with very few viral genes being expressed.
- One of these genes encodes a microRNA which works to prevent cell death, maintaining the latent infection.
- Other genes encodes the latency-associated transcripts (LATs).
- Viral persistence in latently infected ganglia lasts for the lifetime of the host.



Herpes simplex viruses



- **Latent infection**

- The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes.
- HSV-specific immunity limits local viral replication, so that recurrent infections are less extensive and less severe.
- Many recurrences are asymptomatic, reflected only by viral shedding in secretions.



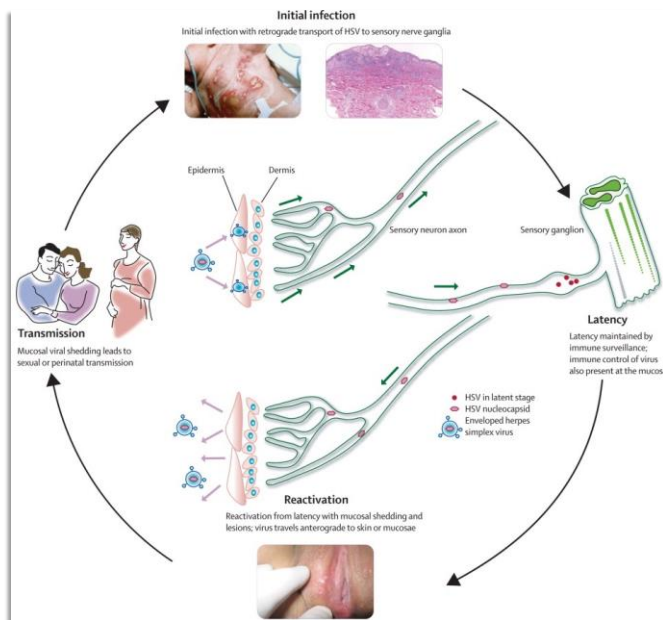
Herpes simplex viruses



- **Latent infection**
- ❖ **Provocative stimuli can reactivate virus from the latent state, including:**
 - *Axonal injury.*
 - *Fever.*
 - *Physical or emotional stress.*
 - *Exposure to ultraviolet light.*



Herpes simplex viruses

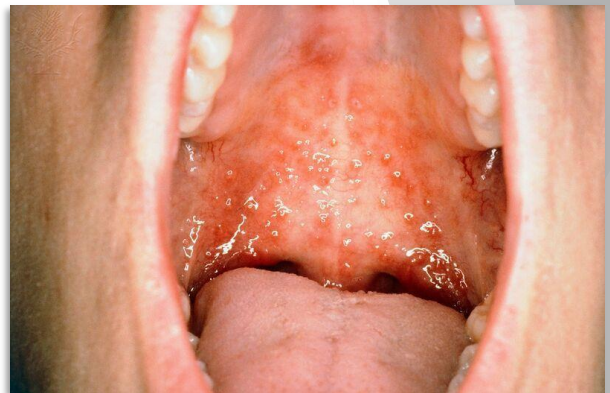




Herpes simplex virus disease



- **Primary/recurrent oropharyngeal disease**
 - *Gingivostomatitis.*
 - *Pharyngitis.*
 - *Mononucleosis-like syndrome.*
 - *Herpes labialis (cold sores).*

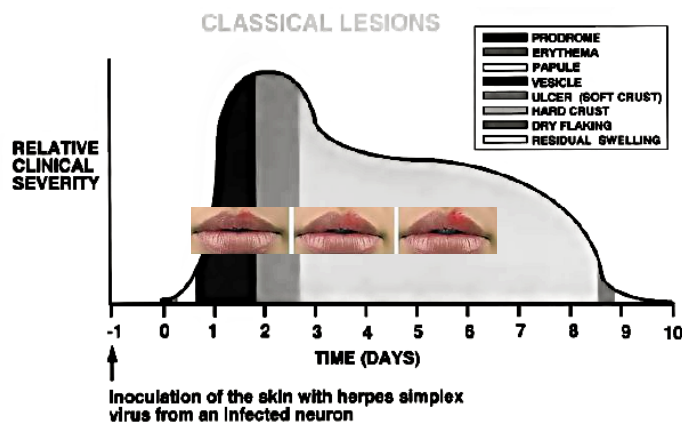




Primary/recurrent oropharyngeal disease



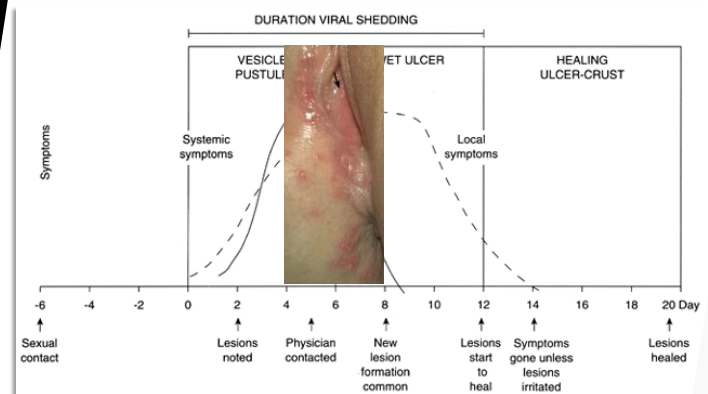
- ✓ The incubation period ranges from 2-12 days, with a mean of 4 days.
- ✓ The duration of clinical illness may be from 2-3 weeks.





Primary/recurrent genital disease

Symptomatic primary genital infection is the most severe, lasting about 3 weeks.





Primary/recurrent genital disease



- **Genital herpes:**
 - In females: Excruciatingly painful lesions in the vulva, perineum, buttocks, cervix, and/or vagina associated with inguinal adenopathy and dysuria.
 - In males: Lesions involving the glans penis or the penile shaft with extragenital lesions of the thigh, buttocks, and perineum.
 - Proctitis can occur in male homosexuals.



Primary/recurrent genital disease



- **Genital herpes:**
 - Recurrences of genital herpetic infections are common and tend to be mild.
 - Recent evidence documented the increase in the frequency of genital (HSV-1) compared with genital (HSV-2) infection. This trend has been seen both in Europe, Australia and in the US.
 - Oral shedding of HSV-2 is infrequent.



Neonatal herpes simplex virus infection

- The estimated incidence of neonatal HSV infection is 1 in 3,000 to 1 in 5,000 deliveries per year.
- May be acquired in utero, during birth, or after birth.
- Neonatal herpes infections are almost always symptomatic.
- The overall mortality rate of untreated disease is 50%.
- Many survivors of severe infections are left with permanent neurologic impairment.

Toxoplasma
others
Rubella
CMV
Herpes





Herpes simplex keratoconjunctivitis



- HHV-1 infections may occur in the eye, producing severe keratoconjunctivitis.
- Recurrent lesions of the eye are common and appear as **dendritic keratitis** or corneal ulcers or as vesicles on the eyelids.
- Keratitis may end up in blindness.





Herpes simplex skin infections

- Usually manifest as **eczema herpeticum** in patients with underlying atopic dermatitis.
- Disseminated HSV infections have been also reported among wrestlers (**herpes gladiatorum**).





Herpes simplex skin infections



- Herpetic whitlow is an infection of a distal phalanx.
- Manifests in painful swelling and non-purulent vesicles.
- Herpetic whitlow follows direct inoculation (exogenous or autogenous) or reactivation of latent virus.





Infections of the immunocompromised host



- Immunocompromised patients are at increased risk of developing severe HSV infections.
- These include patients immunosuppressed by disease or therapy.
- Patients with deficient cellular immunity suffer more frequent and more severe HSV infections.
- Herpes lesions may spread and involve the respiratory tract, esophagus, and intestinal mucosa.
- In most cases, the disease reflects reactivation of latent HSV infection.



Herpes simplex virus infections of the CNS



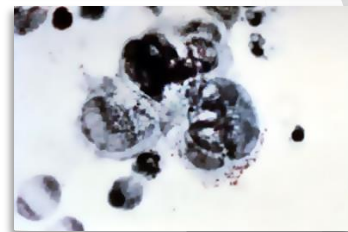
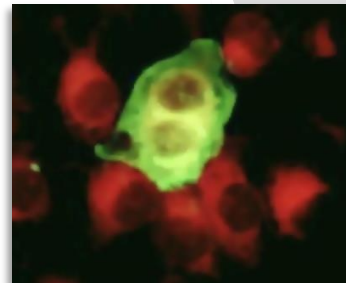
- HSV encephalitis is one of the most devastating of all HSV infection.
- It is considered the most common cause of sporadic, fatal encephalitis in the US.
- The disease carries a high mortality rate.
- Aseptic meningitis is a common occurrence in individuals with primary genital HSV infections.



Herpes simplex virus diagnosis



- Clinical diagnosis.
- Virus isolation is a definitive diagnostic method (samples include: skin scrapings, throat swab, CSF).
- PCR detection of viral DNA.
- Cytopathology with Giemsa stain of scrapings (Tzanck smear).
- Serology.





Herpes simplex virus infections treatment



- Nucleoside analogues: acyclovir, valacyclovir, penciclovir and famciclovir.
- All nucleoside and nucleotide analogues must be activated by phosphorylation usually to the triphosphate form to exert their action.
- Mechanism of action: Inhibition of viral genome replication through inhibiting the viral polymerase.



Herpes simplex virus infections treatment



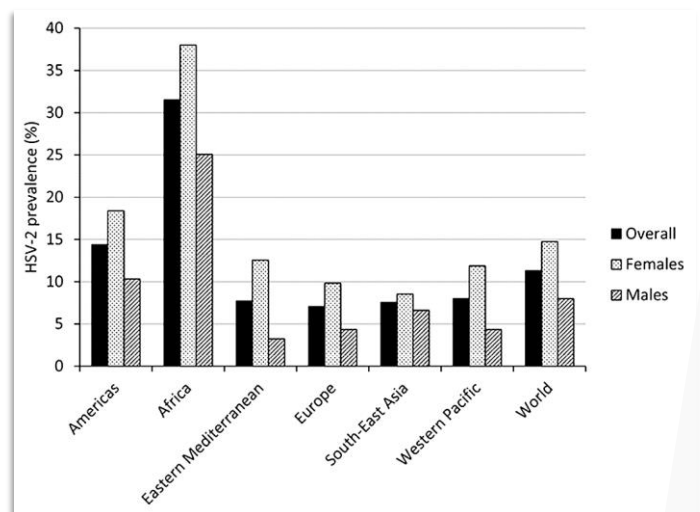
- The virus thymidine kinase is much more potent compared to the cellular kinases in activating the drug, therefore, it is more efficient in virus-infected cells.
- Treatment is important in herpes encephalitis, neonatal herpes, and disseminated infections in immunocompromised patients.
- Despite treatment, HSV remains latent in sensory ganglia.
- Drug-resistant virus strains may emerge.



Epidemiology of *herpes simplex virus*

In 2012, an estimated 3.7 billion people under the age of 50, or 67% of the world population, had HSV-1 infection (WHO).

The overall prevalence of HSV-2 among 15–49 year olds world-wide in 2012 is estimated to be 11% (over 400 million people).





Herpes simplex virus infections prevention and control



- Educational efforts must be developed for adolescents and those at greatest risk.
- Surgical abdominal delivery.
- Hospital staff: Temporary removal of personnel who have cold sores is advocated for clinical services.
- Experimental vaccines.



Varicella zoster virus VZV



- Zoster was derived from a Greek word meaning belt.
- Shingles was derived from a Latin word meaning belt.
- The virus is highly contagious.





Features of VZV infection



- VZV infects T lymphocytes and epithelial cells, while latency takes place in dorsal root ganglia.
- Primary infection causes varicella (chickenpox), and reactivation leads to zoster (shingles).
- Zoster can be complicated by chronic pain and other neurological and ocular disorders (E.g. meningoencephalitis, and keratitis).
- VZV is transmitted via the airborne route, mostly from skin lesions.



Features of VZV infection



- Varicella (chickenpox) is highly communicable and is a common epidemic disease of childhood (most cases occur in children under 10 years of age).
- Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. Ten to 20 percent of adults will experience at least one zoster attack during their lifetime, usually after the age of 50.
- The route of infection is the mucosa of the upper respiratory tract or the conjunctiva.



Features of VZV infection

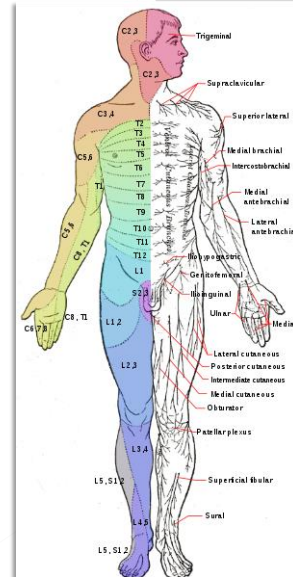


- Following initial replication in regional lymph nodes, primary viremia spreads virus and leads to replication in liver and spleen.
- Secondary viremia involving infected mononuclear cells transports virus to the skin, where the typical rash develops.
- VZV replication and spread are limited by host humoral and cellular immune responses. Interferon may also be involved.



Features of VZV infection

- The skin lesions of zoster are histopathologically identical to those of varicella.
- As a rule, the distribution of lesions in the skin corresponds closely to the areas of innervation from an individual dorsal root ganglion.





Varicella (Chickenpox)

- Subclinical varicella is unusual.
- The incubation period: 10–21 days.
- Malaise and fever are prodromal, followed by rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa.
- Successive fresh vesicles appear in crops, so all stages of macules, papules, vesicles, and crusts may be seen at one time. The rash lasts about 5 days.
- Complications are rare in normal children, and the mortality rate is very low.





Zoster (Shingles)



- Zoster occurs in immunocompromised persons.
- It starts with severe pain in the area of skin or mucosa supplied by the sensory nerves and ganglia.
- Within a few days, a crop of vesicles appears over the skin supplied by the affected nerves. The trunk, head, and neck are most commonly affected.
- The most common complication of zoster in the elderly is postherpetic neuralgia which is a protracted pain that may continue for months.



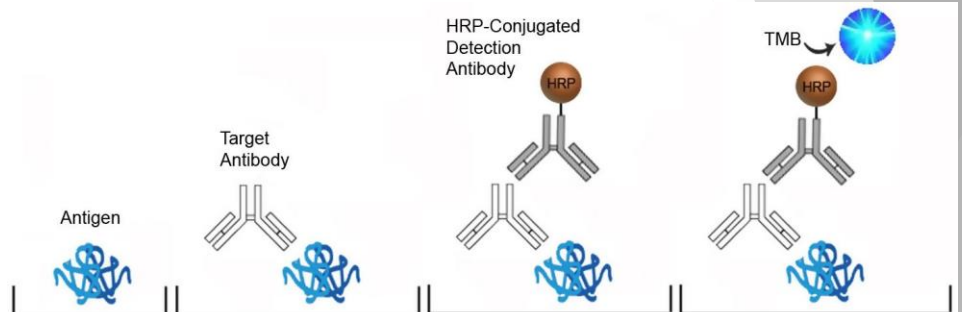
Zoster (Shingles)





Diagnosis of VZV infection

- Clinical.
- Tzanck smear.
- DFA.
- Serology.
- PCR.





Treatment



- Varicella in normal children is a mild disease and requires no treatment.
- Varicella-zoster immune globulin can be used to prevent the development of the illness.
- Several antiviral compounds provide effective therapy for varicella, including acyclovir, valacyclovir and famciclovir.
- Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults.
- Acyclovir does not appear to prevent postherpetic neuralgia.



Prevention



- A live attenuated varicella vaccine is highly effective at inducing protection from varicella in children (80–85% effective), but less so in adults (70%).
- The duration of protective immunity induced by the vaccine is unknown, but is probably long term.
- Varicella infections can occur in vaccinated persons, but they are usually mild illnesses.
- Zoster vaccines are available and can reduce the rates of shingles.



Thanks for listening...