SHEET NO.

MICROBIOLOGY (Virology)

DOCTOR 2019 | MEDICINE | JU

DONE BY :

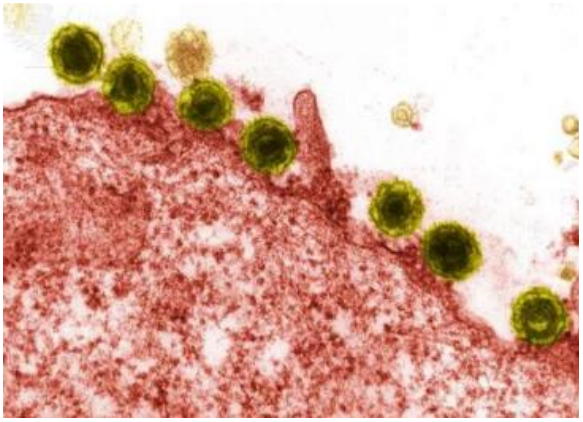
SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

DOCTOR :

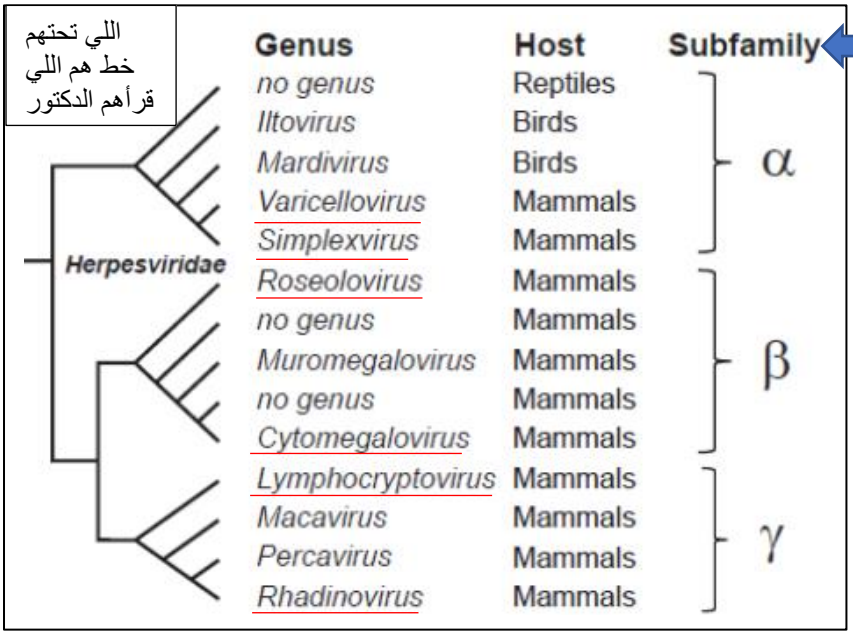
Herpesviridae:

The first family of viruses that can cause diseases
e.g. - herpes simplex virus
- **varicella** zoster virus (the cause of **chickenpox)**
- epstien-Barr viruses (onco viruses)
- Kaposi's sarcoma (onco viruses)



transmission electron micrograph for herpesviruses emerging from t-cells

اللي تحتهم خط هم اللي قرأهم الدكتور



Important Notes on the chart:
→ Herpesviridae can affect other living organisms rather than humans such as birds and reptiles.
→ Herpesviridae have 3 subfamilies: α, β and γ.
→ Roseolovirus and Cytomegalovirus are viruses that infect humans from β subfamily
→ rhadinovirus (specially human herpes virus-8) and lymphocryptovirus (specially Epstein–Barr virus) from γ subfamily infect humans

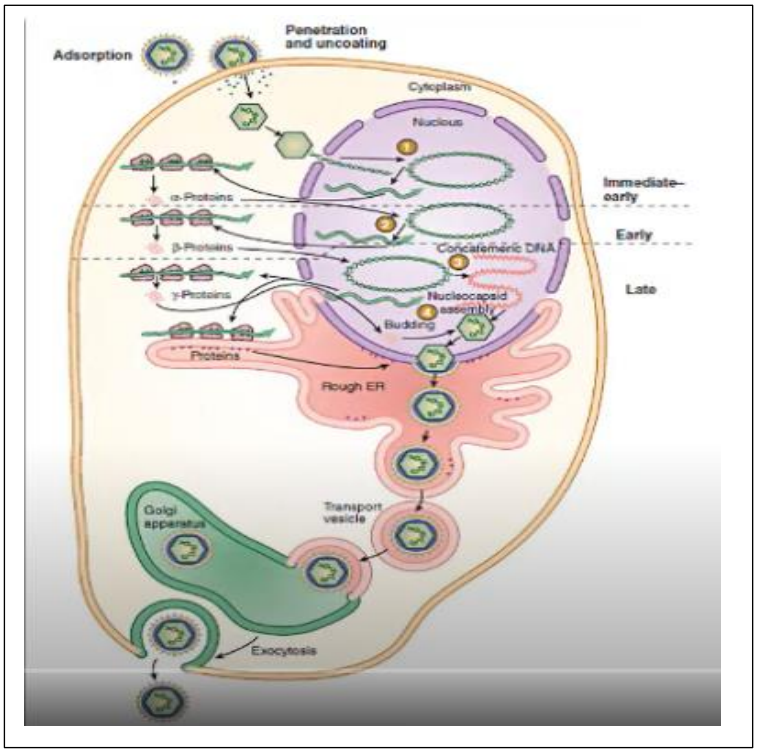
note: number of herpesviruses that effect human are 9

ICTV Classification		common name		genome size
Human HV 1	HHV-1	Herpes simplex virus [type] 1	αS	152
Human HV 2	HHV-2	Herpes simplex virus [type] 2	αS	155
Human HV 3	HHV-3	Varicella-zoster virus	αV	125
Human HV 4	HHV-4	Epstein-Barr virus	γL	172
Human HV 5	HHV-5	Cytomegalovirus (CMV)	βC	236
Human HV6A	HHV-6A	HHV-6 variant A	βR	159/170
Human HV6B	HHV-6B	HHV-6 variant B	βR	162/168
Human HV 7	HHV-7		βR	145
Human HV 8	HHV-8	Kaposi's sarcoma–associated HV (KSHV)	γR	170/210

→What are the characteristics of Herpesviridae?
1. Have Double stranded, linear and large DNA genome (it's size about 125 – 240 kilobases

and reaches sometimes 295), the genome is retraited sequences
2. Virion: Spherical, 150-200 nm in diameter (quite large) (icosahedral) it has 20 faces.
3. Have an envelope that is acquired from the nuclear membrane, it contains viral glycoproteins (G- Glycoproteins) and fc receptors (fc receptors are taken from cell proteins)
4. Proteins: More than 35 proteins in virion (even more)
5. Have a region called tegument: a region between the capsid and the envelope, this region doesn't have a standard shape, it contains proteins that helps the virus after it emerges inside the cell to release it's genome so it can reach the nucleic acid to make replication and translation
6. Replication occurs in the nucleus, and the budding is from nuclear membrane
7. Outstanding characteristics:
a) Encode many enzymes
b) Establish life-long latent infections(متى ما دخل الجسم ما رح يطلع منه بأي طريقة)
c) Persist indefinitely in infected hosts
d) Frequently reactivated in immunosuppressed hostsظ
(لأنهt-cells عادة هم اللي بحاولوا يسيطروا عالوضع وانه الفايروس ما يرجع ينشط، بس مع كبر العمر مثلًا بصير في مشاكل مناعية فالفايروس بسهولة ممكن يرجع ينشط لو دخل الجسم بما انه بظل فيه)
e) Some cause cancer like epv, and many causes lymph privative diseases because they immortalize b-cells

Replication cycle

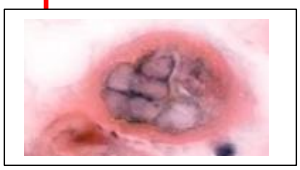


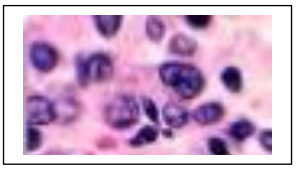
a. binding to a specific receptor (there are more than one receptor that are specific to Herpesviridae
b. Penetration
c. uncoating, so the virus will lose the envelope and the capsid will enter with assistant of proteins on the tegument
d. the virus will reach the nucleus and release it's genome
e. there will be translation of immediate-early genes that will produce α – proteins.
f. α – proteins will help in regulation and translation of early genes that will produce β – proteins.
g. β – proteins are important in the replication of the viral DNA, the viral DNA will produce concatemeric DNA (A continues DNA strand that contains more than one copy of a genome for more than one virus)
h. late transcription and translation will occur and give us γ – protein
I. concatemeric DNA will undergo excision to be in corroborated with γ – protein that will form the capsid, the capsid will enclose the viral genome and bud from the nuclear membrane and enter the Rough ER

J. Some proteins will associate with the virus in the rough ER
K. A transport vesicle will move the virus to the Golgi apparatus and then it will exit the cell by exocytosis
L. When using the ribosomes of the cell to produce viruses, ribosomes can't produce normal proteins for cell function, After a while of that the cell will die and lyse so huge number of viruses will exit from it, most viruses exit the cell after it dies
→ While replication, part of the results of transcription of herpes viruses shut down the inter-virion effect, so the cell won't recognize the virus (an evasion mechanism of the immune response)
→ inter-virion is important to prevent the anti-viral states response of the neighboring cells.

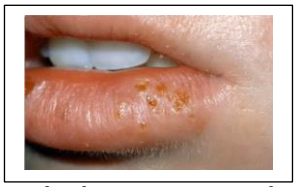
Cytopathic effect of the Herpesviridae

1. intra-nucleus basophilic Inclusion
2. Rounding of cells
3. Mito-nucleated cell formation

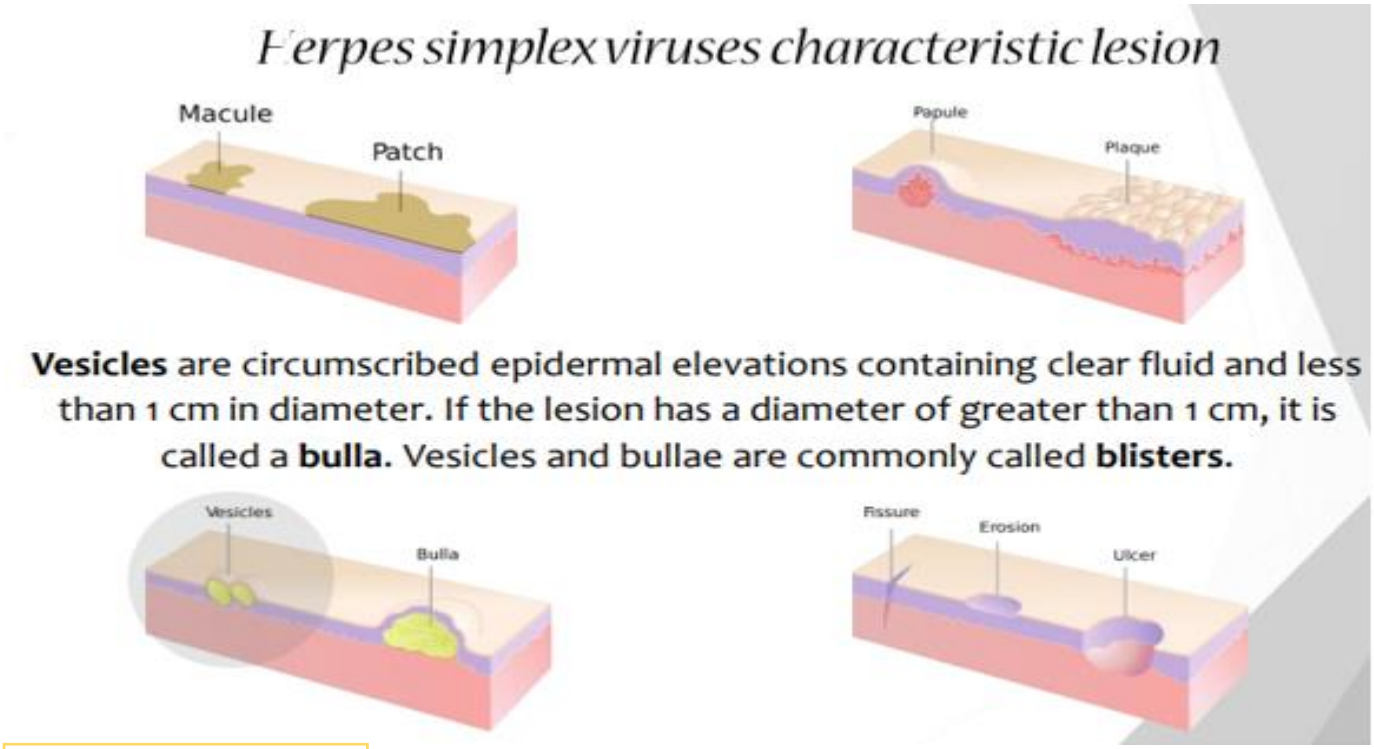




Diseases caused by Herpesviridae



first: Herpes simplex virus :
causes oral herpes labialis, it effects different parts of the face and the ear, and it causes redness and sensation, then forms papules then forms vesicles that are filled with fluid (very characteristic symptom), then the vesicles open forming crusting
→ how transmission occurs?
mainly because of intimate contact between an ill individual and a healthy individual
→ It mainly effects children, especially countries with poor hygiene
→ Many of cases don't form vesicles, as high infections come from type-1 viruses (although type-1 can form vesicles sometimes)
→ The virus could transmit also because of sexual activity, type-2 mainly transfer by this way
→ The virus have genetic and cytosolic infections, at last they will destroy the cells
→ Pathologic changes are :
1. Necrosis of infected cells (Direct and primary effect of virus)
2. Inflammatory response (Secondary effect of the virus)
→ The target cells of these viruses are skin and mucous membranes
→ It's hard to differentiate between clinical symptoms of type-1 and type-2, but not impossible as we can differentiate between them by looking to the genetic material
→ Pathologic changes are similar for primary and recurrent infections but vary in degree, reflecting the extent of viral cytopathology عدد الفيروسات الي تعرضلها الشخص المصاب



Primary infection

o Viral replication occurs first at the site of infection (usually skin and mucosal membranes).
o HSV then invades local nerve endings and is transported (capsid is only transported) by retrograde axonal flow to dorsal root ganglia.
o After further replication, latency is established.
o Oropharyngeal infections result in latent infections in the trigeminal ganglia.
o Genital infections lead to latently infected sacral ganglia.

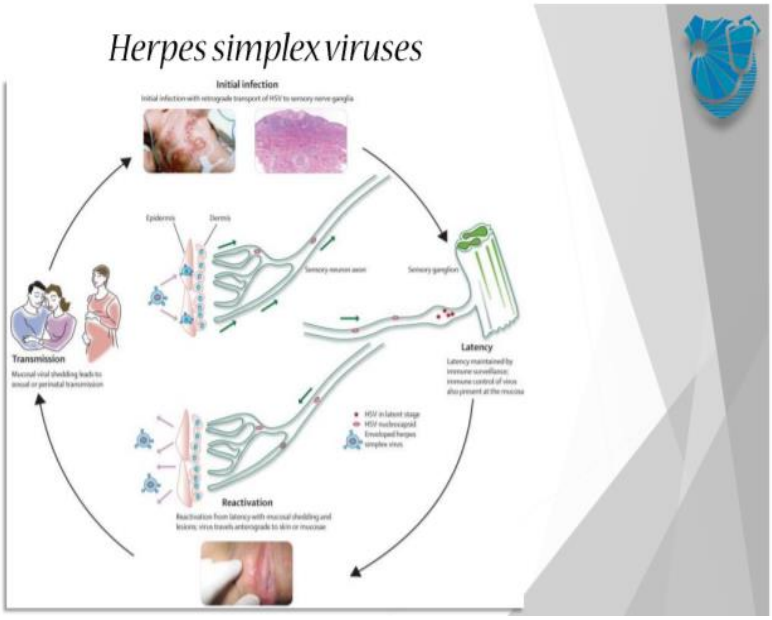
Latent infection

o Virus resides in latently infected ganglia with very few viral genes being expressed.
o One of these genes encodes a microRNA which works to prevent cell death, maintaining the latent infection.
o Other genes encodes the latency-associated transcripts (LATs), preventing the immune attack against the virus. When certain viral genes gets activated then the virus will produce late transcript to synthesize structural product that activate the latent virus to get back to site of infection and replicate there to revel the symptoms of the injury or disease
o Viral persistence in latently infected ganglia lasts for the lifetime of the host.

Latent infection (current attack)

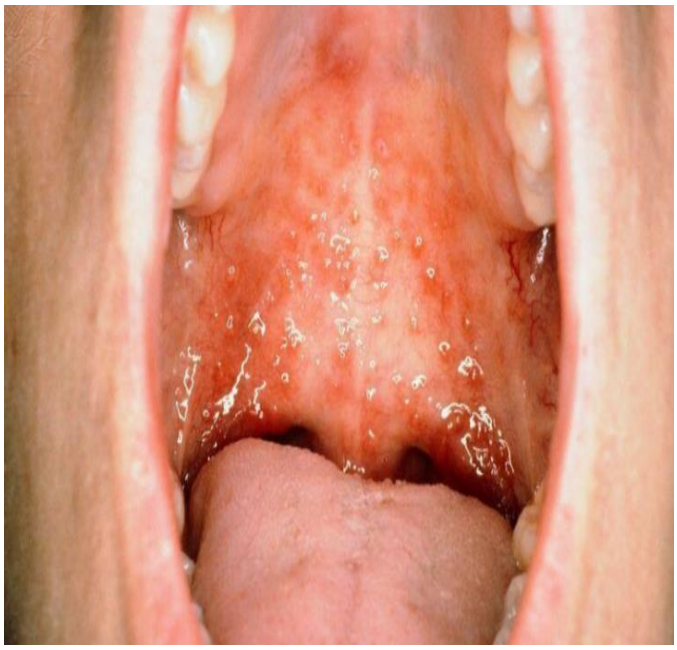
o The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes.
o HSV-specific immunity limits local viral replication, so that recurrent infections are less extensive and less severe.
o Many recurrences are asymptomatic, reflected only by viral shedding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

❖ Provocative stimuli can reactivate virus from the latent state, including:
o Axonal injury.
o Fever.
o Physical or emotional stress (affect cellular immunity)
o Exposure to ultraviolet light.



The virus will recognize the target cell in the epidermis and make infection and through the sensory nerve ending the virus will transport into the sensory ganglia and it still dormant due to activation of latency transcript, and some ribonucleic acids keep check of the primary infection site where the immune system is already activated there and when the immune response decrease there would be activation of the latent virus that get back to the primary infection site and induce the lesion

1) Primary/recurrent oropharyngeal disease



o Gingivostomatitis (gum & mouth swelling) .

o Pharyngitis (differential diagnosis of pharyngitis is HSU).

o Mononucleosis-like syndrome:

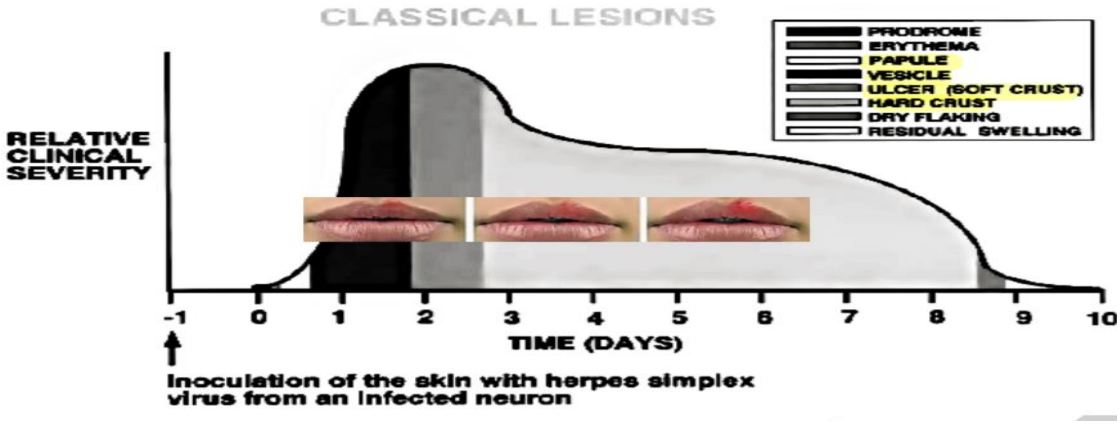
1. fever
2. pharyngitis
3. cervical lymphadenopathy

o Herpes labialis (cold sores).

- It's of two types:
  - type 1 HSV cause symptoms that are above waist diseases
  - type 2 HSV cause symptoms that are below waist diseases

Primary/ recurrent oropharyngeal diseases

- ✓ usually caused by type 1 HSV
- ✓ usually asymptomatic & recurrent infections have higher probability to be asymptomatic
- ✓ 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.



2)primary / recurrent genital diseases

- ✓ Usually caused by type 2 HSV
- ✓ symptomatic primary genital infection is the most severe, lasting about 3 weeks.
- ✓ Have higher prevalence than, oropharyngeal
- ✓ Why type 1 can cause both diseases unlike type 2:
  * type 1 immunity can sometimes protect against type 2
  * oral sexual practices are getting higher so type I can develop genital infections
  * type 1 is usually transmitted by regular transmission touching, so a lot of people are infected and have immunity against type 1 specially in developing counties.
  *Type 2 is sexually transmitted and unlikely to be transmitted easily between people

Primary/recurrent genital disease

Genital herpes

o In females: Excruciatingly painful lesions in the vulva, perineum, buttocks, cervix, and/or vagina associated with inguinal adenopathy and dysuria.
o In males: Lesions involving the glans penis or the penile shaft with extragenital lesions of the thigh, buttocks, and perineum.
o Proctitis can occur in male homosexuals
o Recurrences of genital herpetic infections are common and tend to be mild.
o 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.
o Oral shedding of HSV-2 is infrequent.

Why type 1 can cause both diseases unlike type 2
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Neonatal herpes simplex virus infection

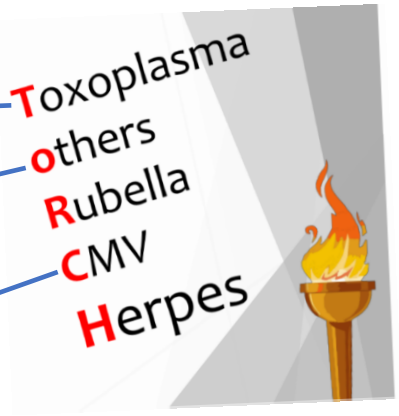
- The estimated incidence of neonatal HSV infection is 1 in 3,000 to 1 in 5,000 deliveries per year.
- May be acquired in utero, during birth, or after birth (may lead to disseminated – infection)
- Neonatal herpes infections are almost always symptomatic.
- The overall mortality rate of untreated disease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

MAIN CONGENATAL INFECTIONS:

parasites

hepatitis B, syphilis

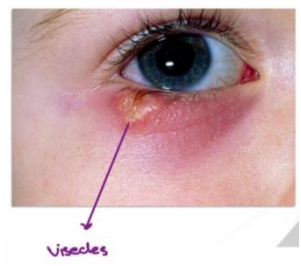
most common cause of congenital infections

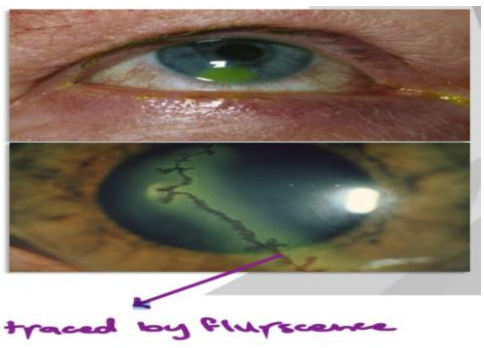


Herpes simplex keratoconjunctivitis

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

- DENDRITIC KERATITIS ARE : y pathognomonic for type 1 HSU

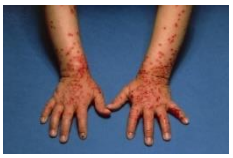




Herpes simplex skin infections

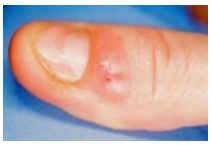
Usually manifest as

1) **eczema herpeticum** in patients with **underlying atopic dermatitis**.
2) **herpes gladiatorum**: Disseminated HSV infections have been also reported among **wrestlers** المصارعون



NOTE: If someone has an intact skin (without any traumas) he will has a resistance against the infection of HSV1, otherwise he will be infected.
-In oral mucosa, there will be an infection in all cases, even if the oral mucosa is intact.

3) **Herpetic whitlow:** is an infection of a distal phalanx which manifests in painful swelling and non-purulent vesicles, it follows direct inoculation (exogenous or autogenous) or reactivation of latent virus.
exogenous: like in health care workers (especially in dentists)
endogenous: from the person himself; like when a child puts his **oral herpes infected finger** in his **mouth**, he will be infected with herpetic whitlow.



Infections of the immunocompromised host

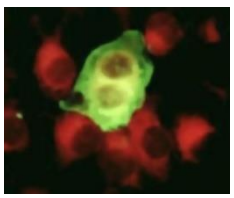
- Immunocompromised patients are **at increased risk** of developing severe HSV infections, These include patients immunosuppressed by disease or therapy, it means that patients with deficient cellular immunity suffer more frequent and more severe HSV infections.
- Herpes lesions may spread and involve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

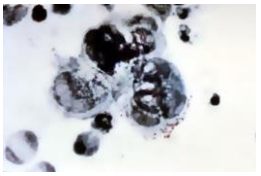
Herpes simplex virus infections of the CNS

- **HSV-1** 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 and it carries a high mortality rate.
- Aseptic meningitis -caused by **HSV-2**- is a common occurrence in individuals with primary genital HSV infections.

Herpes simplex virus diagnosis

1) **Clinical** diagnosis.
2) Virus isolation is a definitive diagnostic method (samples include: skin scrapings, throat swab, CSF).
   - *Meningitis is diagnosed by CSF (Cerebrospinal Fluid).*
   - *Encephalitis is diagnosed by imaging diagnosis.*
3) **PCR** detection of viral DNA.
4) **Cytopathology** with Giemsa stain of scrapings (Tzanck smear).
5) **Serology:** by looking for IgM, IgG, usually made by the ELISA (Enzyme-Linked Immunosorbent) method.





Herpes simplex virus infections treatment

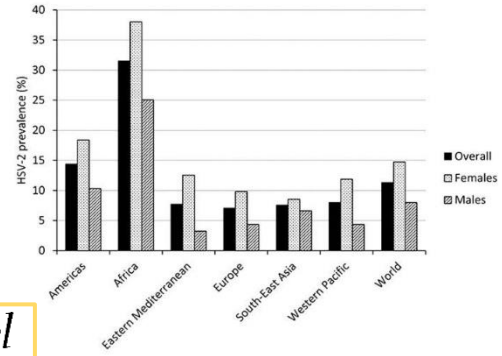
HSV Treatment options:

- Nucleoside analogues: 1)**acyclovir**, 2)**valacyclovir**, 3)**penciclovir** and 4)**famciclovir**, they inhibit viral genome replication by inhibiting the viral polymerase (the mechanism).
- All nucleoside and nucleotide analogues must be activated by phosphorylation usually to the triphosphate form to exert their action.

-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**.
-Treatment of herpes simplex is NOT CURATIVE, but in normal people this infection is self-limited (أسبوعين تلات وبروح)
-Despite treatment, HSV remains latent in sensory ganglia.
-Drug-resistant virus strains may emerge. (the only problem in the treatment)

Epidemiology of herpes simple 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 years old world-wide in 2012 is estimated to be 11% (over 400 million people).
-occurs in females more than males.

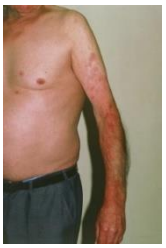


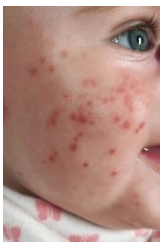
Herpes simplex virus infections prevention and control

1) **Educational efforts** must be developed for adolescents and those at greatest risk.
2) **Surgical abdominal delivery**. (in case the mother is infected).
3) **Hospital staff**: Temporary removal of personnel who have cold sores is advocated for clinical services.
4) **Experimental vaccines. There is NO approved vaccine UNTIL NOW!**

Varicella zoster virus VZV

Zoster was derived from a Greek word meaning belt, **Shingles** was derived from a Latin word meaning belt (they give the same meaning for the same infection).
-VSV primary infection causes the chickenpox جدري الماء
While in the reactivation state it makes the shingles (zoster) الحزام الناري
-The virus is **highly contagious:** attack rates are very HIGH.



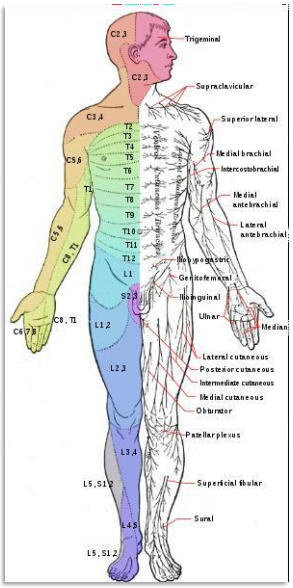


Features of VZV infection

- VZV infects **T lymphocytes and epithelial cells**, while latency takes place in **dorsal root ganglia**.
- Zoster can be complicated by chronic pain and other neurological and ocular disorders (E.g. meningoencephalitis, postherpetic neuralgia, and keratitis).
- VZV is transmitted via the **airborne route**, mostly from skin lesions.
  NOTE: The viral causes of meningitis are: HSV, VZV reactivation state, mumps virus, enteroviruses.

- 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 حالات فردية because it results from reactivation, 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.

- 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, THAT'S WHY who infected once by zoster will not be infected again UNLESS the virus is reactivated.

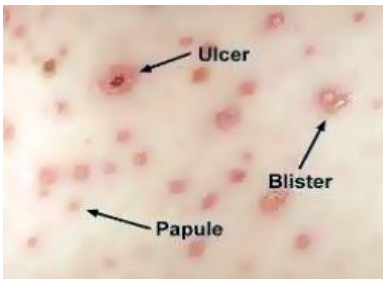


NOTE: VZV & HSV used glycosaminolglycans (GAGs) & other receptors like immunoglobulins super family and integrin proteins, these receptors have ubiquitous distribution, so there is a lot number of cells that can be infected

- The skin lesions of zoster are histo-pathologically 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.

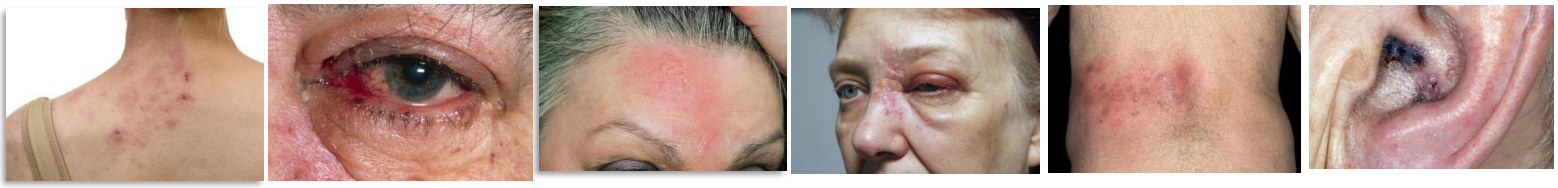
Varicella (Chickenpox)

- 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. (central spread من محور الجسم إلى الأطراف)
- 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.
- Infectious virus.



Zoster (Shingles)

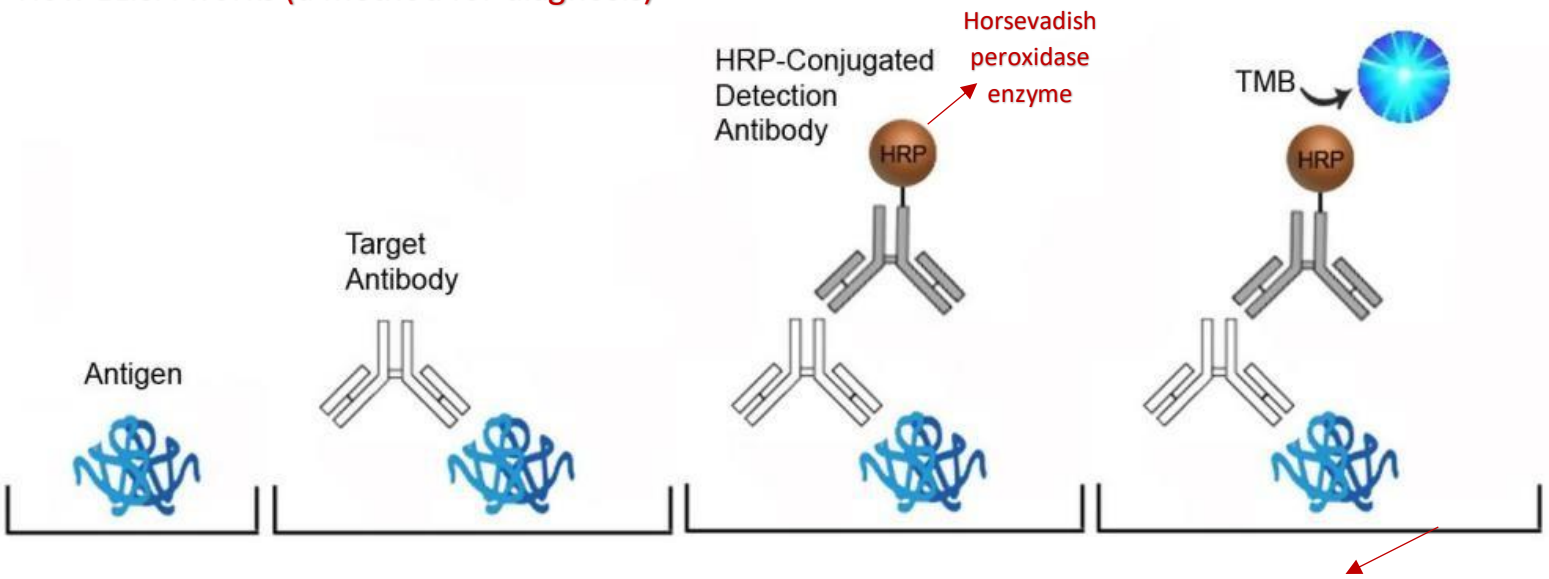
- Zoster occurs in immunocompromised persons.
- It starts with severe pain in the area of skin or mucosa supplied by the sensory nerves and ganglia.
- Within a few days, a crop of vesicles appears over the skin supplied by the affected nerves. The trunk, head, and neck are most commonly affected.
- The most common complication of zoster in the elderly is postherpetic neuralgia which is a protracted pain that may continue for months. بتروح الحويصلات وبضل في وجع لأكتر من 3 شهور



Diagnosis of VZV infection

Clinical.
Tzanck smear.
DFA (direct fluorescent antibody)
Serology.
PCR.

How ELISA works (a method for diagnosis)



We make WASHING after each step, so if there is no antibodies the enzyme will be washed away, while if there is antibodies the enzyme will link the antibody and the blue colored substrate will appear (if there is no antibodies no enzymes will be linked and no color will appear)

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: there is a **neuro-damage** so the antivirus will not be effective for the management of the 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.