MICROBIOLOGY

بسم الله الرحمن الرحيم

Final – Lecture 3

Herpesviruses

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

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7- Herpesviruses

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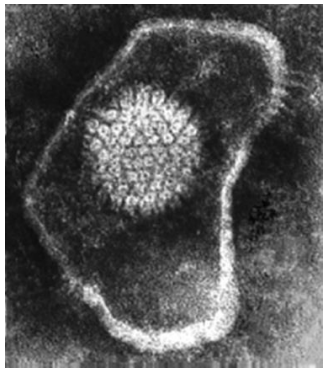
Objectives

- Discuss the morphology, epidemiology, pathogenesis, clinical presentation, laboratory diagnosis and management of:

1. Herpes Simplex virus Type 1 (HSV-1)
2. Herpes Simplex virus Type 2 (HSV-2)
3. Epstein Barr virus (EBV)
4. Cytomegalovirus (CMV)
5. Varicella Zoster virus (VZV)
6. Human Herpes virus 6 (HHV-6)
7. Human Herpes virus 8 (HHV-8)

Introduction



- Herpes Viruses are a leading cause of human viral diseases, second only to influenza and cold viruses
- The outstanding property of herpesviruses is their ability to establish lifelong persistent infections in their hosts and to undergo periodic reactivation

  Latency is the most important property of it.

  After causing a primary infection, it establishes latency with the host allowing for reactivation.
- Reactivation is more likely to take place during periods of immunosuppression and in the elderly
- All herpesviruses have identical morphology and cannot be distinguished from each other under electron microscopy.

Classification

Group	Biological characteristics	Members
Alpha herpesviruses	fast-growing, cytolytic, establish latent infections in **neurons**	HSV-1, HSV-2, VZV
Beta herpesviruses	slow growing, cytomegalic, become latent in **secretory glands and kidneys**	CMV, HHV-6, HHV-7
Gamma herpesviruses	Variable, lymphoproliferative, e latent in **lymphoid cells**	EBV, HHV-8

General properties

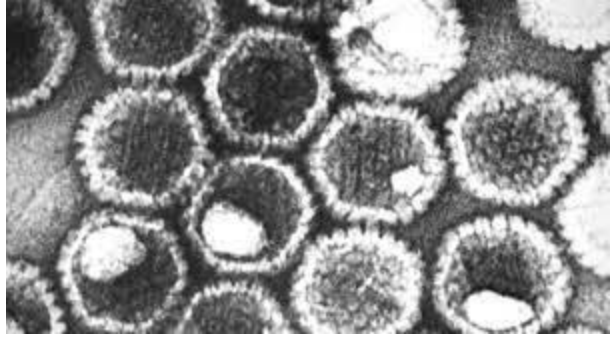


TABLE 33-1 Important Properties of Herpesviruses

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

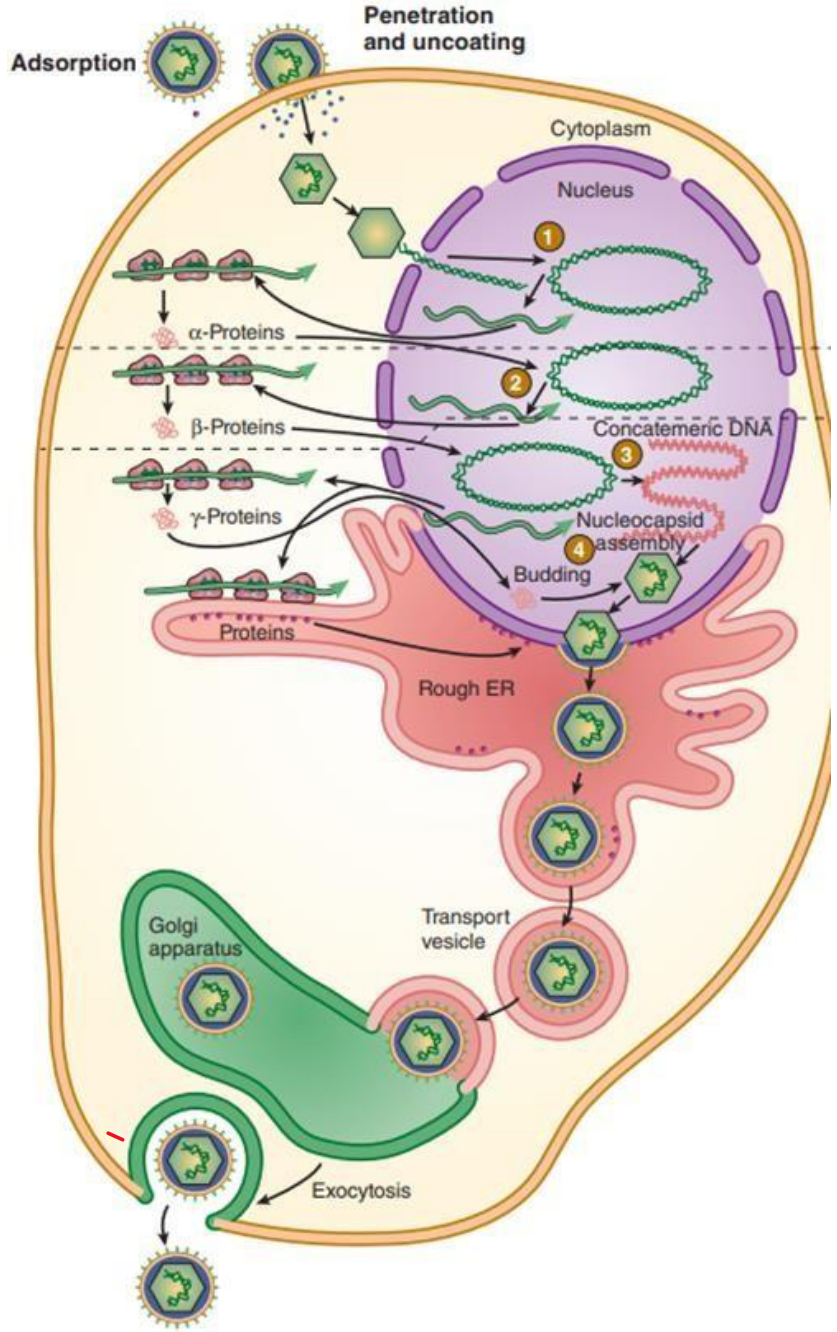
Its envelope contains fragments of nuclear envelope instead of the plasma membrane

Replication

1. α-Proteins, products of immediate-early genes, stimulate transcription of early genes.
2. β-Proteins, products of early genes, function in DNA replication, yielding concatemeric DNA.
3. γ-Proteins, products of late genes and consisting primarily of viral structural proteins, participate in virion assembly

They encode a large number of enzymes/proteins (70-200)

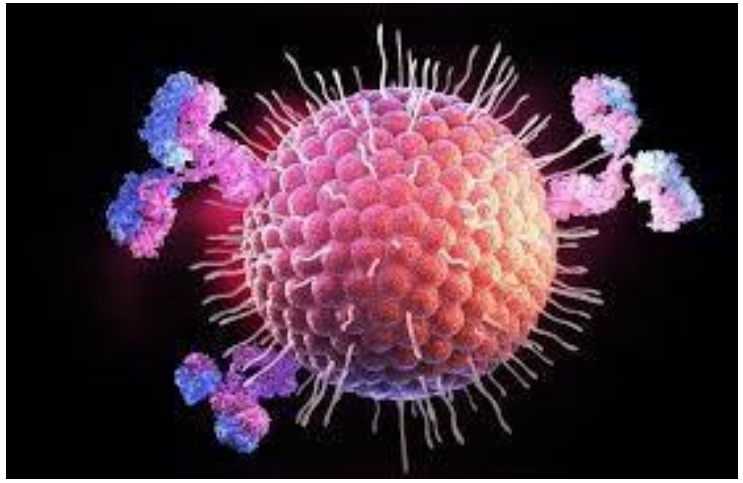
It enters the nucleus through nuclear pores, its linear DNA becomes circularized, synthesizes proteins(sequential) in stages α-proteins(immediate early), β-proteins(early), γ-proteins9 late), following replication-> DNA returns to its original form; long, linear, and repeated, and it's called **concatemeric DNA**



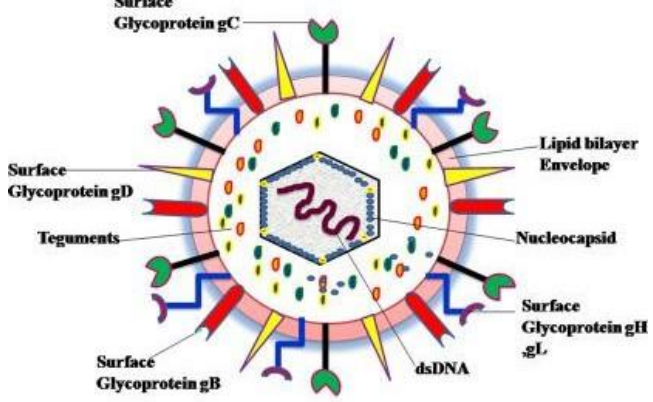
Important clinical viruses

- There are 25 families in the Herpeotoviridae but only 7 of them infect man:
  - Herpes Simplex virus Type 1 (HSV-1)
  - Herpes Simplex virus Type 2 (HSV-2)
  - Epstein Barr virus (EBV)
  - Cytomegalovirus (CMV)
  - Varicella Zoster virus (VZV)
  - Human Herpes virus 6 (HHV-6)
  - Human Herpes virus 8 (HHV-8)

1- Herpes Simplex Viruses (HSV)



Properties



Herpes simplex virus

- Belong to the alpha herpesvirus subfamily of herpesviruses
- HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons
- Type 1 is associated with oropharyngeal lesions (above the belt) while Type 2 infects the genital mucosa (below the belt), though the anatomical specificity of these viruses is diminishing
- Classically, HSV-1 is spread by contact with infected saliva and HSV-2 is transmitted sexually
- The genome of HSV-1 and HSV-2 share 50 - 70% homology.
- They also share several cross-reactive epitopes with each other.

Epidemiology

- HSV is spread by contact, as the virus is shed in saliva, tears, genital and other secretions.
- By far the most common form of infection results from a kiss given to a child or adult from a person shedding the virus.
- There are 2 peaks of incidence, the first at 0 - 5 years and the second in the late teens when sexual activity commences.
- About 10% of the population acquires HSV infection through the genital route and the risk is concentrated in young adulthood.
- Following primary infection, 45% of orally infected individuals and 60% of patients with genital herpes will experience recurrences.

The only one that has a vaccine is Varicella Zoster virus (VZV) because the similarity between herpesviruses is in the morphological properties but their genome and internal structure is diffrent

Pathogenesis and Pathology

- Because HSV causes cytolytic infections, pathologic changes are due to necrosis of infected cells and inflammation(ulcers)
- During the primary infection, HSV spreads locally and a short-lived viremia occurs. Spread to the craniospinal ganglia (trigeminal or sacral ganglia) through retrograde axonal flow and establishes latency. Peripheral axons transport signals anterograde(brain-> extremities) but the virus goes in the opposite direction, and inside the nerve, it's latent and doesn't replicate.
- Virus resides in latently infected ganglia in a nonreplicating state and persists for life
- Reactivation/recurrence is triggered by physical or psychological stress, infection, fever, or ultraviolet and sunlight
- The virus transits via axons back to the peripheral site, and replication proceeds at the skin or mucous membranes

Clinical Manifestations

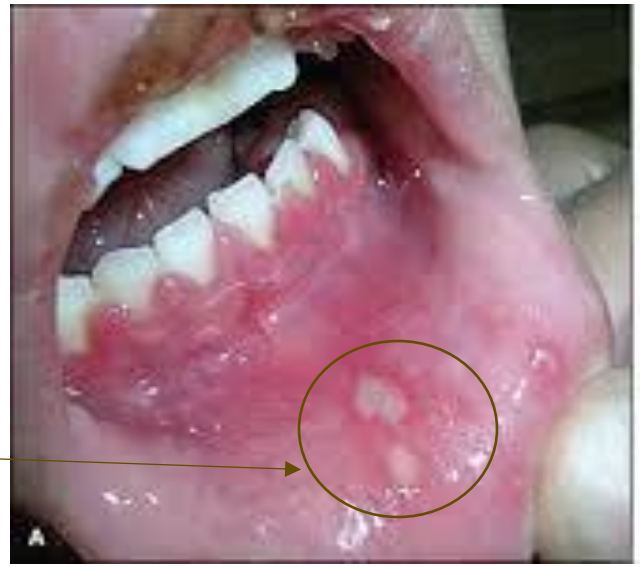
HSV is involved in a variety of clinical manifestations which includes;-

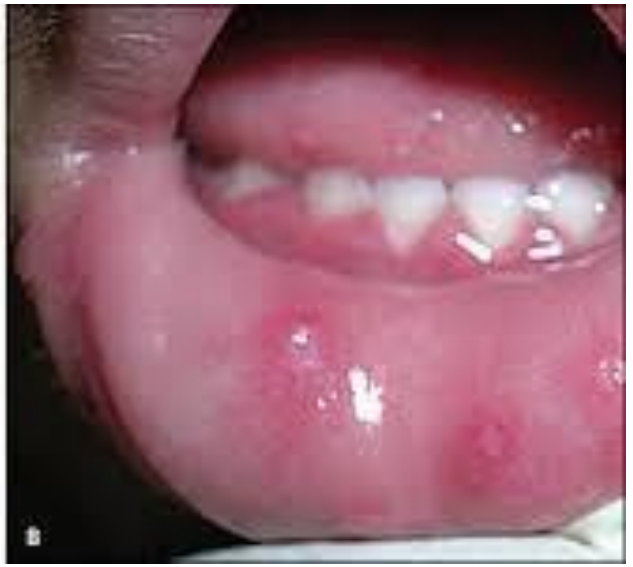
1. Acute gingivostomatitis(inside the mouth)
2. Herpes Labialis (cold sore)
   (outside of the mouth)
3. Ocular Herpes
4. Herpes Genitalis
5. Meningitis/Encephalitis
6. Neonatal herpes(active maternal genital herpes infection during delivery, the virus may infect the baby, and travel to its brain causing encephalitis, and then possible death).

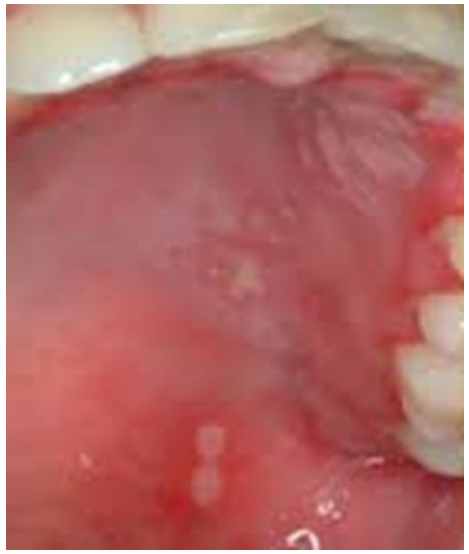
Oral-facial Herpes (HSV-1)

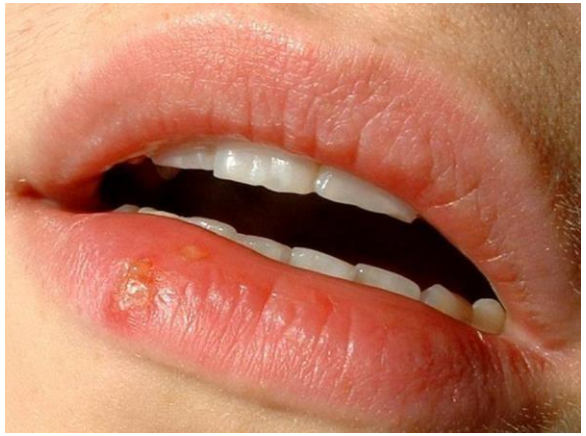
- **Acute Gingivostomatitis**
  - The commonest manifestation of primary herpetic infection.
  - The patient experiences pain and bleeding of the gums. 1 - 8 mm ulcers with necrotic bases are present. Neck glands are commonly enlarged accompanied by fever.
  - Usually a self-limiting disease that lasts around 13 days.
- **Herpes labialis (cold sore)**
  - Following primary infection, 45% of orally infected individuals will experience reactivation.
  - Herpes labialis (cold sore) is a recurrence of oral HSV.
  - A prodrome of tingling, warmth, or itching at the site usually heralds the recurrence. About 12 hours later, redness appears followed by papules and then vesicles.

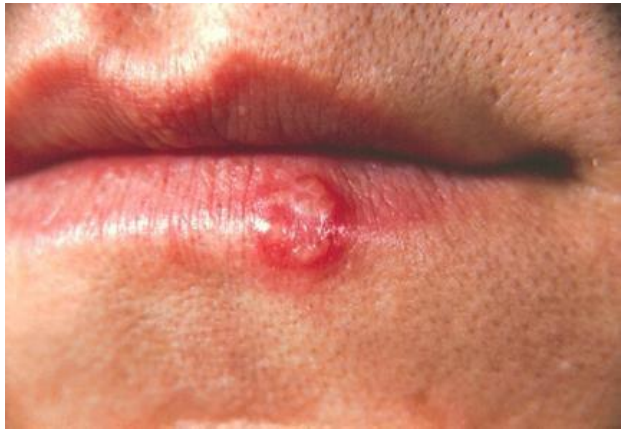
Most common placement

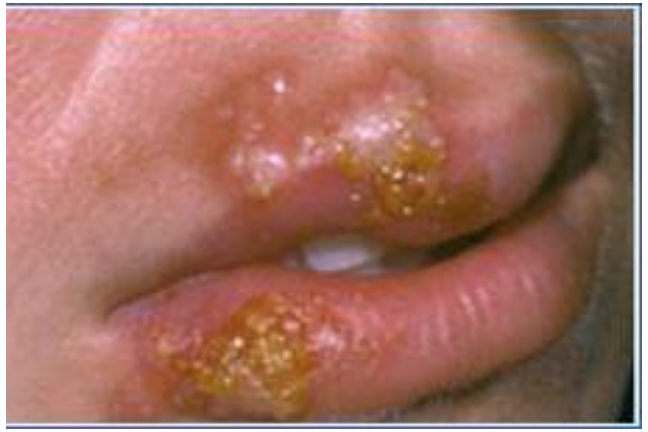












Ocular herpes

- HSV infections may occur in the eye(its mucosal membrane), producing severe keratoconjunctivitis
  (inflammation of both keratao= cornea, conjunctiva)
- Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids
- With recurrent keratitis permanent opacification and blindness might occur

Progression of symptoms

Genital Herpes (HSV-2)

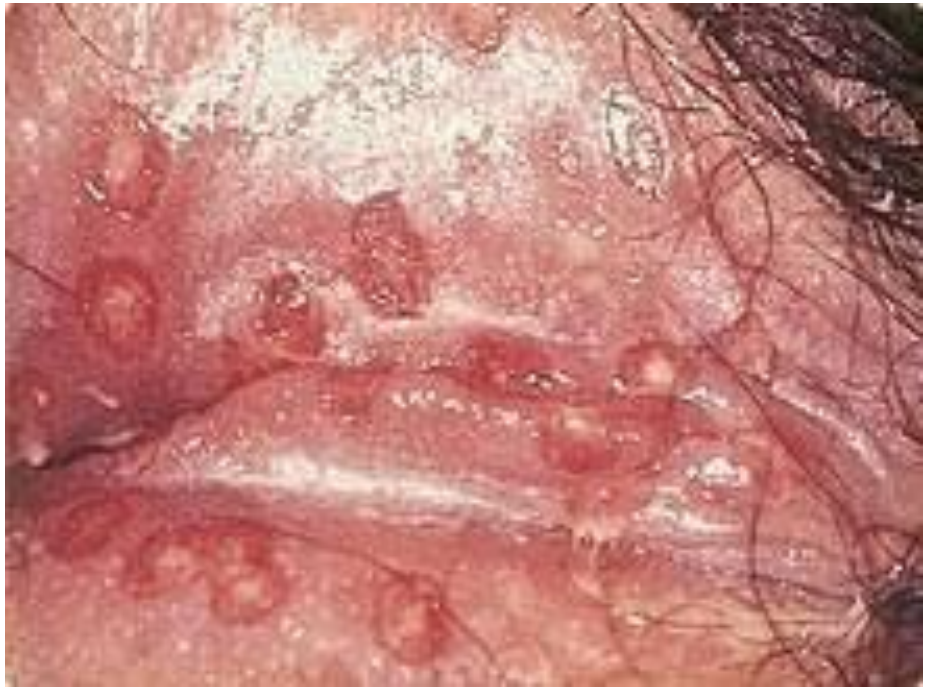
around genital area

- Genital herpes is characterized by vesiculoulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female
- lesions are very painful and may be associated with fever, malaise, dysuria, and inguinal lymphadenopathy.
- The lesions of genital herpes **ulcers** are particularly prone to secondary bacterial infection
- 60% of patients with genital herpes will experience recurrences.
- Recurrent lesions in the perianal area tend to be more numerous and persists longer.

Primary lesion → Latency in the sacral nerve (sacral ganglion) → recurrent lesions

Lesions may start around the cervix or vagina as (1) then be transmitted around perianal area as (3).

(1)



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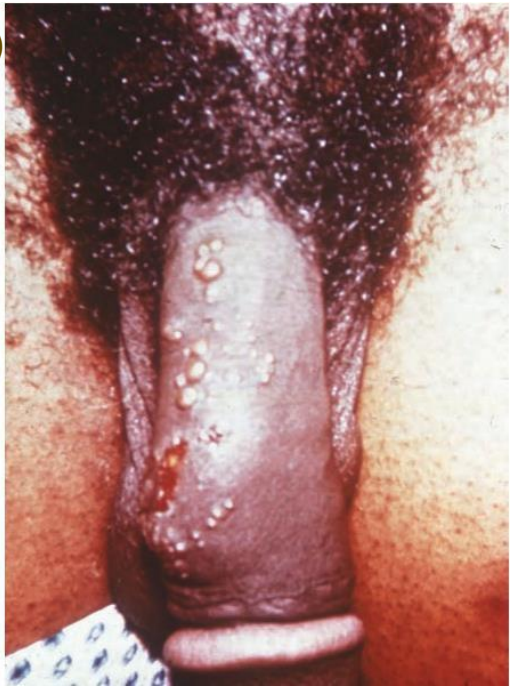

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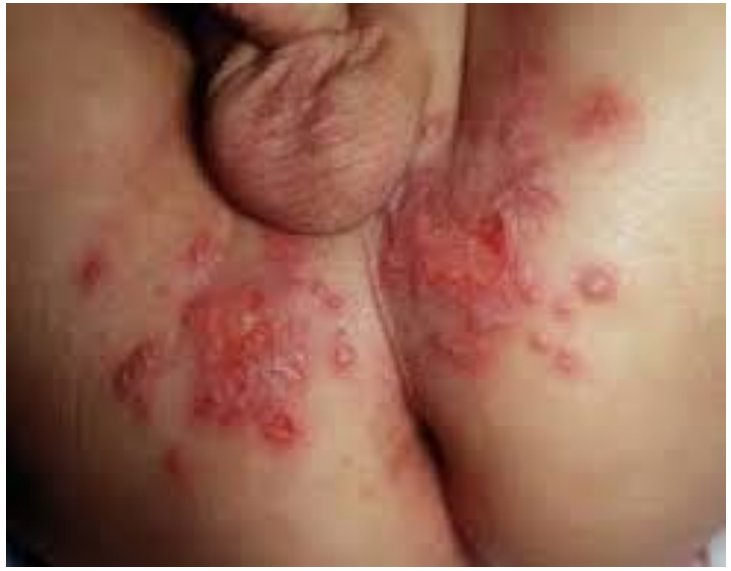


(4)

Herpes Simplex Encephalitis

HSV may reach the brain either through nerves or via blood –if dissemination occur when the virus is in the circulation- ,causing damage of brain cells resulting in death .

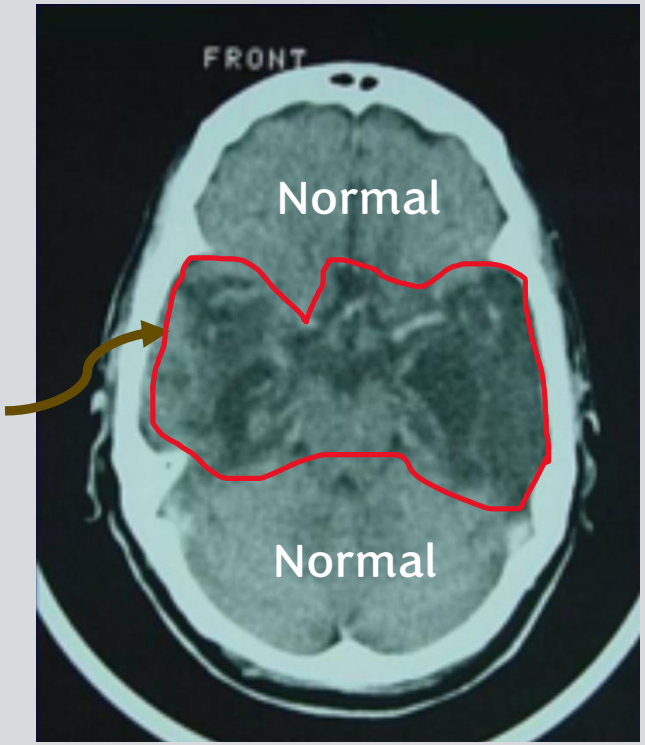
- Herpes Simplex meningitis or encephalitis is one of the most serious **(life threatening) and rare** complications of herpes simplex disease. There are two forms:

1. Neonatal **(neonatalmieningoencephalitis)** – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100% **(more dangerous in neonate)**. Transmission of virus during delivery through infected genital secretions from the mother. **Treatment: it can be prevented by undergoing caesarean section instead of labor delivery to avoid the contact between the baby and the ulcer .**

2. Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults **(especially immunocompromised)** . It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.

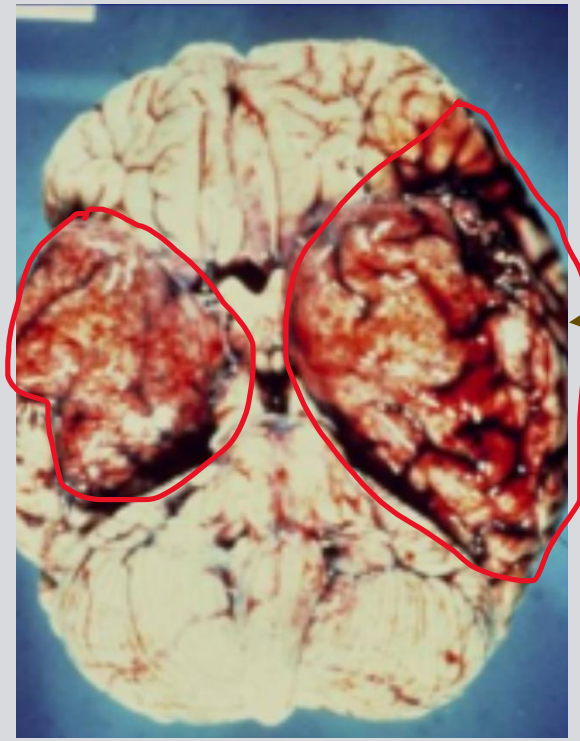
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given **in all cases of suspected HSE before laboratory results are available.**

Herpes Simplex Encephalitis



Affected cells

CT scan



Damage /Lysis/
Liquefiation of cells.

Autopsy

Further Notes
in next slide.

Laboratory Diagnosis

- Direct Detection
  - Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV
  - Immunofluorescence of skin scrappings - can distinguish between HSV and VZV
  - PCR - now used routinely for the diagnosis of herpes simple encephalitis **(most common and useful method)**
- Virus Isolation
  - HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days for a result to be available.
- Serology
  - Not that useful in the acute phase because it takes 1-2 weeks before antibodies appear after infection.
- Cytopathology
  - Multinucleated giant cells and ballooning of cells. **(cytopathic effect)**

- 90-95% of diagnosis is done by noticing the clinical symptoms; so in case of cold sore, taking swab and making investigation is not required every recurrent lesion, but in case of transmission of the virus to the eye or the brain it is a must to make investigations and to start the treatment even before appearance of laboratory results.

- The sample could be taken from an active ulcer, by a swab for the eye or CSF for the brain, but it can't be taken from the ganglion because there is no viral replication.

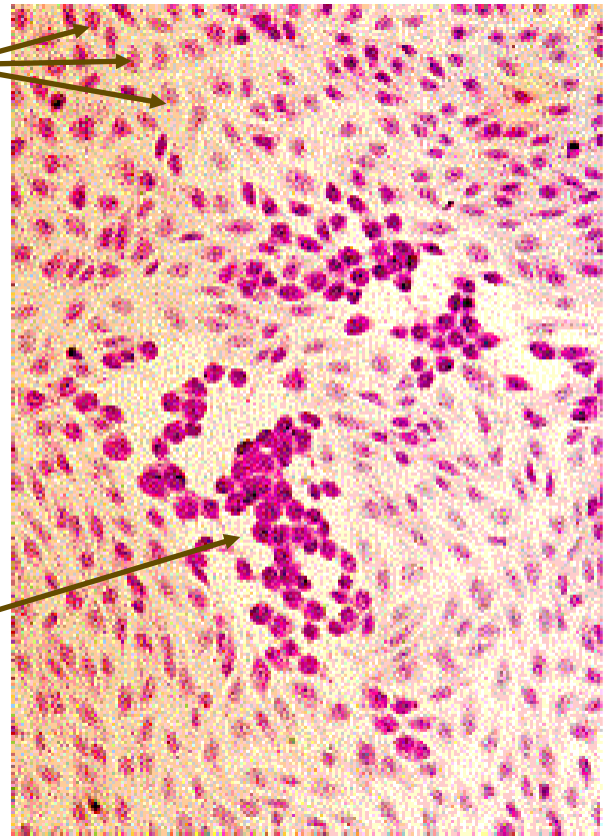
- Genital herpes: when primary lesion occurs, a swab could be taken for further investigation to exclude other sexual diseases.

- Antibodies test (IgG and IgM) is not very useful.

Microscopically:
Necrosis, WBCs, cytomegaly.

Normal cells

The virus exist here and perform "cytopathic effect"



Cytopathic Effect of HSV in cell culture: Note the ballooning of cells.

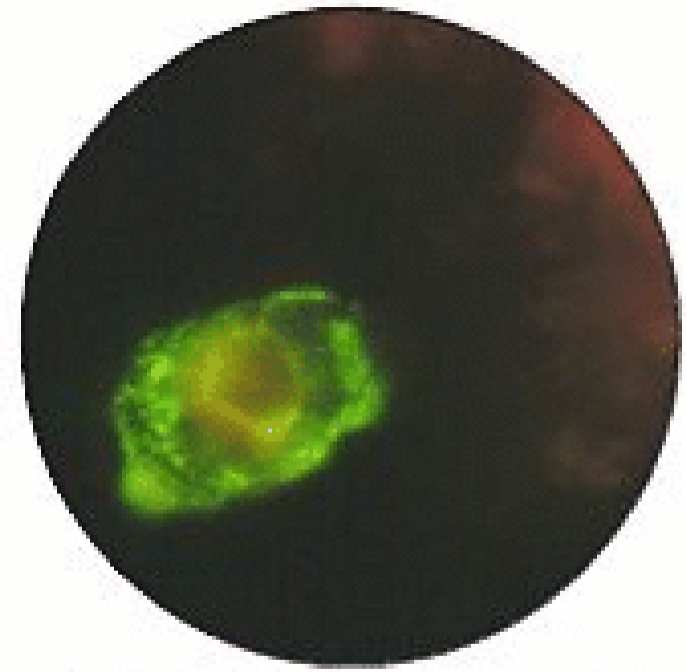
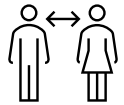


Fig. 3. HSV-infected epithelial cell from skin lesion (DFA)

Positive immunofluorescence **(specific)** test for HSV antigen in epithelial cell.

Management and prevention



- **Prevention**

1. Avoiding contact with individuals with lesions; however, virus may be shed asymptomatically (symptoms & recurrence lesions differ among individuals). – especially for children because they are more prone to infection than adults who have IgG.

2. Safe sexual practices.
3. Cesarean section delivery to minimize contact of the infant with infected maternal genital secretions.
4. Triggers must be avoided as much as possible.

There is NO vaccine.

Management and prevention

- At present, there are only a few indications of antiviral chemo-

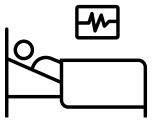
therapy (Oral – tablets / IV) :

1. the primary infection is especially severe
2. dissemination
3. sight is threatened
4. herpes simplex encephalitis

- Acyclovir – this is the drug of choice.

- For cold sore (Labialis) & Gingivostomatitis : internal ulcer (ointment) / external ulcer (cream).

- Ocular (eye) & HSE (brain): IV Acyclovir 

In case of HSE the patient must be admitted to ICU. 

HSE : Herpes Simplex Encephalitis.

Remember:

Acyclovir (Zovirax) :
- A widely used antiviral with main implications in the treatment of herpes.
- Inhibits viral DNA polymerase and terminates viral DNA chain growth.

2- Varicella- Zoster Virus (VZV)

Belongs to alpha group

*Remember:
Attack rate: usually calculated during an outbreak

Attack rate = No new cases of illness during a specified time period / Total population at risk during that specified period

Epidemiology

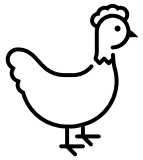
Causes Chickenpox

- Primary varicella is an endemic disease. Varicella is one of the classic diseases of childhood, with the highest prevalence occurring in the 4 - 10 years old age group. (very common but less prevalent that HSV)
- Varicella is highly communicable, with an attack rate* of 90% in close contacts. (Symptoms are severe in adults /community vaccination)
- Most people become infected before adulthood but 10% of young adults remain susceptible.

Although VZV and HSV are from the same group and have the same reactivation mechanism (Primary lesion -> Latency in neurons -> recurrent lesions), but VZV affect the skin -rather than the mucous membranes and conjunctiva- & have less recurrent lesions.

Pathogenesis

- The virus is thought to gain entry via the respiratory tract and spreads shortly after to the lymphoid system.
- After an incubation period of 14 days, the virus arrives at its
- main target organ, the skin. **(causes skin rash (crops skin rash=different types of blisters))**
- Following the primary infection, the virus remains latent in the cerebral or posterior root ganglia. In 10 - 20% of individuals, a single recurrent infection occurs after several decades **as Shingles (الحزام الناري).**
- The virus reactivates in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve, producing a varicellaform rash in the dermatome distribution.

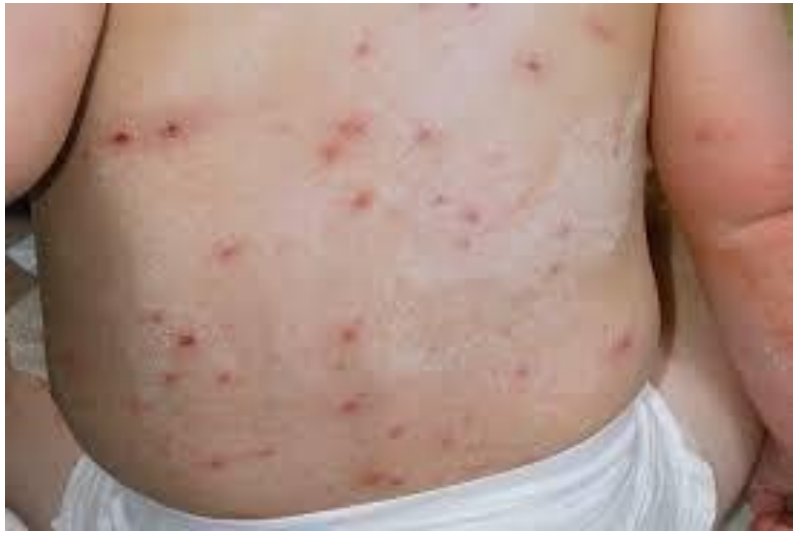


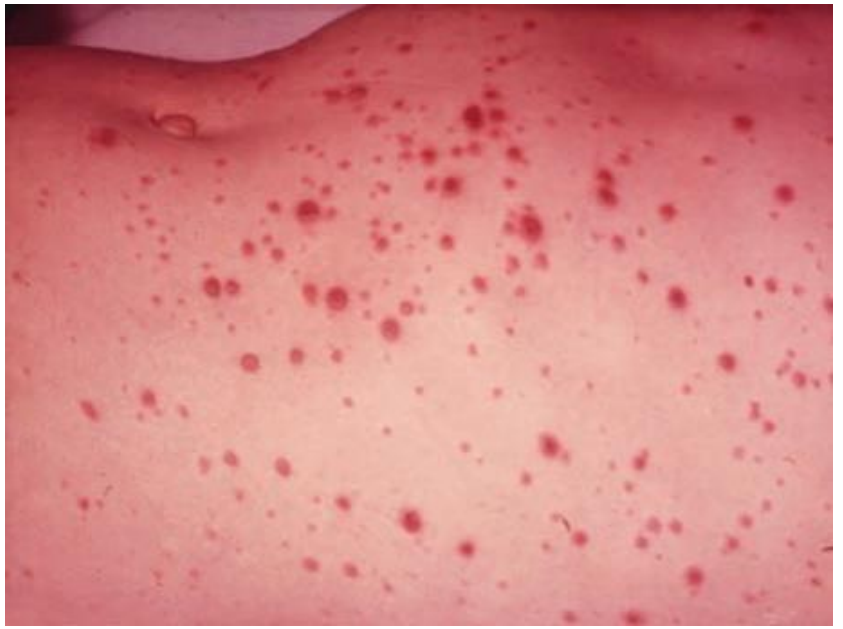
Varicella (chickenpox)

NOT smallpox.

- Primary infection results in varicella (chickenpox)
- Incubation period of 14-21 days
- Presents fever, lymphadenopathy, a widespread vesicular rash.
- The rash appears first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa
- Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time
- The features are so characteristic that a diagnosis can usually be made on clinical grounds alone.
- Complications are rare and may include viral pneumonia, encephalitis, and hemorrhagic chickenpox.

- Chickenpox is NOT the same of Smallpox.
- Smallpox is NOT Chickenpox.
- Chickenpox & Smallpox are different from each other (:

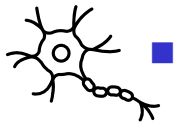




Herpes Zoster (Shingles)

Symptoms: Fever, rash, lympha-denopathy, intensive pain...

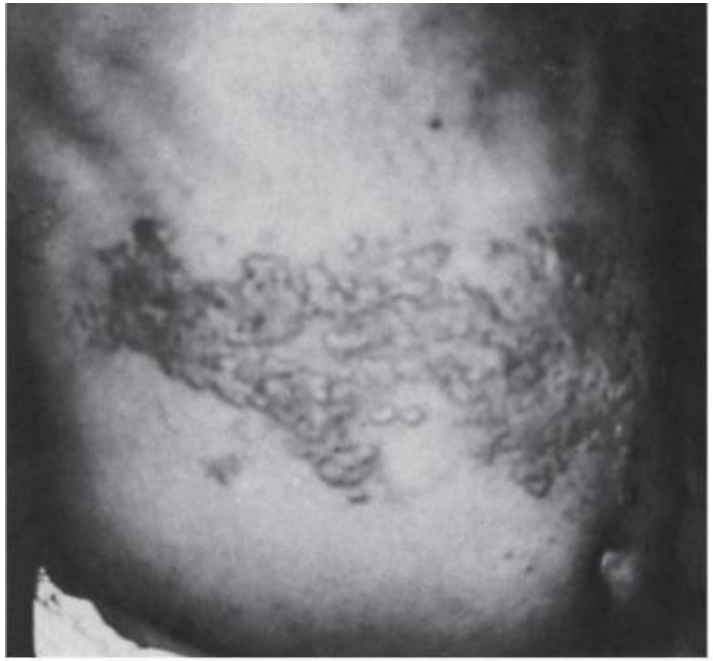
- Herpes Zoster mainly affect a single dermatome of the skin.
- It may occur at any age but the vast majority of patients are more than 50 years of age.

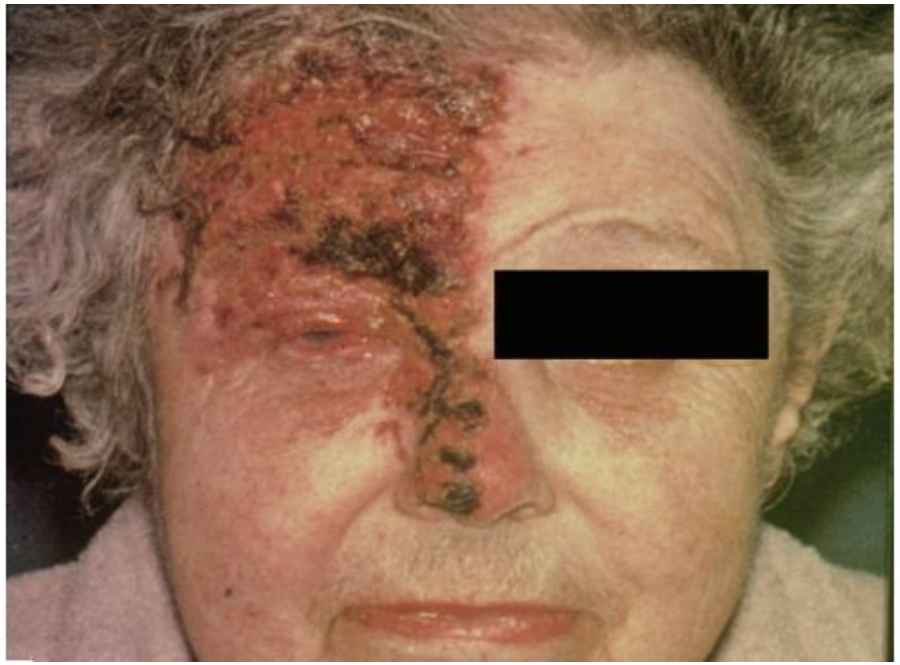


- The latent virus reactivates in a sensory ganglion and tracks down the sensory nerve to the appropriate segment.

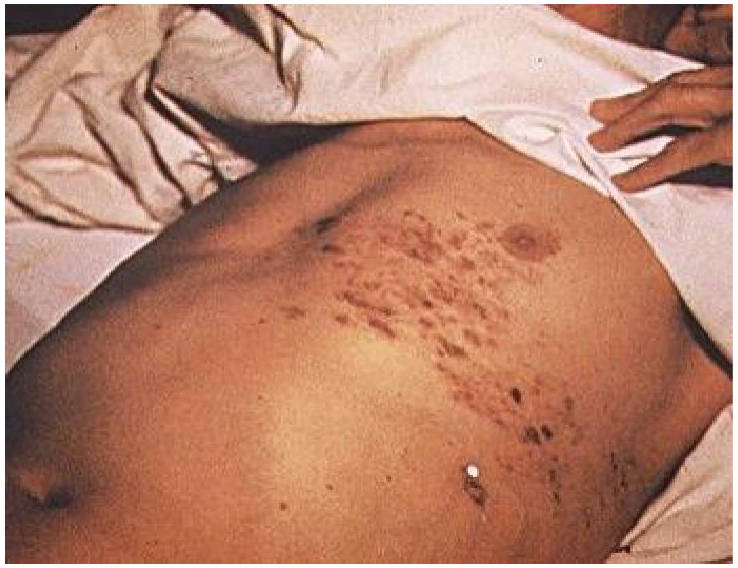
There is a characteristic eruption of vesicles in the dermatome which is often accompanied by intensive pain which may last for months (postherpetic neuralgia) (rash may disappear after a month but the pain persists for longer time)

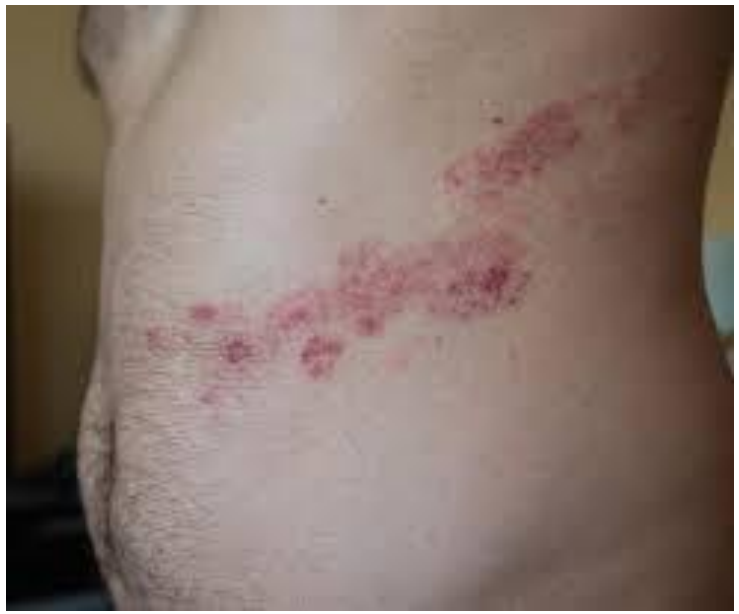
- Herpes zoster affecting the eye and face may pose great problems.
- As with varicella, herpes zoster in a far greater problem in immunocompromised patients in whom the reactivation occurs earlier in life and multiple attacks occur as well as complications.
- Complications are rare and include encephalitis and disseminated herpes zoster.





- After recurrence , shingles become infectious. The first response must be the primary (chickenpox) regardless the age of the patient then the virus will be latent in neurons.
- it doesn't lead to death.





Laboratory Diagnosis (Same of HSV)

The clinical presentations of varicella or zoster are so characteristic that laboratory confirmation is rarely required. Laboratory diagnosis is required only for atypical presentations, particularly in the immunocompromised.

- Virus Isolation - rarely carried out as it requires 2-3.
- Direct detection – electron microscopy for vesicle fluids and immunofluorescence on skin scrappings.
- Serology – The presence of VZV IgM is indicative of a recent primary infection. IgG is indicative of past infection and immunity.
- PCR
- Cytopathology: multinucleated giant cells

Management and prevention

- Uncomplicated varicella is a self-limited disease and requires no specific treatment. However, acyclovir has been shown to accelerate the resolution of the disease.
- Acyclovir should be given promptly to immunocompromised individuals with varicella infection and normal individuals with serious complications such as pneumonia and encephalitis.
- A live attenuated vaccine is available (The only HV that has a vaccine).Recent data suggests that the vaccine is safe. It is given for certain people who are at risk; age: > 50 years , immunocompromised, family history, ...
- Where urgent protection is needed, passive immunization should be given. Zoster immunoglobulin (ZIG) is the preparation of choice but it is very expensive.  + Less recurrence.
- Shingles does not cause death.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي: