



Virology for 2<sup>nd</sup> Year MD Students

# (08) DNA viruses: *Herpesviridae 2*

التي كثر على  
HHV-3  
HHV-4  
HHV-5  
HHV-6 & HHV 7  
HHV-8

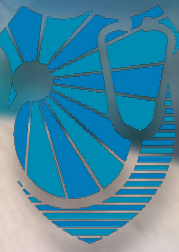
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القاسم المشترك بينهم :  
dsDNA  
Envelope  
Latency & Reactivation  
عند ضعف المناعة

# overview

<i>Virus</i>	الاسم	<i>Tropism</i>	<i>Latency</i>
<i>Varicella Zoster Virus</i>	HHV-3	<i>Epithelial cells</i>	<i>Sensory ganglia</i>
<i>Epstein-Barr Virus</i>	HHV-4	<i>B cells, oral epithelium</i>	<i>B cells</i>
<i>Cytomegalovirus</i>	HHV-5	<i>Almost any cell</i>	<i>Myeloid cells</i>
HHV-6	HHV-6	<i>Many immune cells</i>	<i>PBMCs</i>
HHV-7	HHV-7	<i>CD4+ T cells</i>	<i>PBMCs</i>
<i>Kaposi's Sarcoma-Associated Herpesvirus</i>	HHV-8	<i>B cells</i>	<i>B cells</i>



# Human herpes virus 3 (HHV-3) Varicella zoster virus (VZV)

chickenpox

حزام

← الطفح يسمى على Dermatitis

- Zoster was derived from a Greek word meaning belt.
- Shingles was derived from a Latin word meaning belt.
- The virus is highly contagious. ↙
- Tropism: Epithelial mucosal cells.
- Latency: Sensory neurons (dorsal ganglia).
- Cellular receptors: Heparan sulfate among others.

HS / حس





# Human herpes virus 3 (HHV-3) Varicella zoster virus (VZV)

- Transmission: Respiratory, direct contact *even before symptoms appear* *with lesions*
- 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.

*↳ as a result of the death of T cell*



*كلما زاد العمر كلما زادت الاحتمالية*



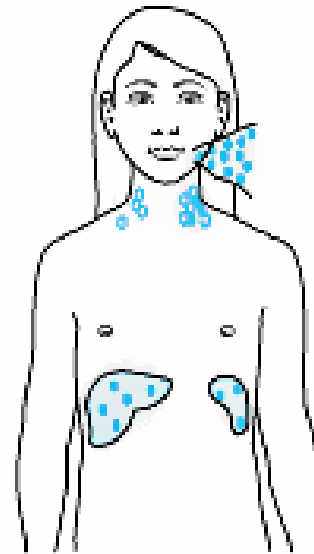


# VZV

## Pathogenesis & Pathology



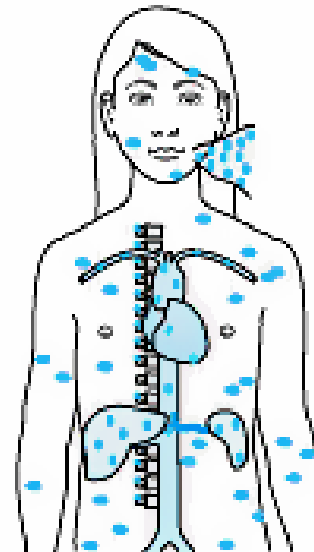
### Incubation period



- { Inoculation of respiratory mucosa
- { Viral replication in regional nodes
- virus-infected cells into capillaries

- { Primary viremia
- replication in liver/spleen

### Acute illness



- { Secondary viremia: mononuclear cell transport to skin and mucous membranes

- { Virus release into respiratory secretions

- { Replication in epidermal cells
- { Virus in dorsal root ganglia

- { VZV specific immunity
- resolution of replication

# Pathogenesis (مهم جداً) → Varicella (Chickenpox)

دخول الفيروس عبر respiratory tract

تكاثر أولي

## Viremia

وصول للجلد → vesicular rash

بعدها الفيروس يدخل الأعصاب → Latency

📌 Latency location: dorsal root ganglia

♦ Reactivation → Zoster (Shingles)

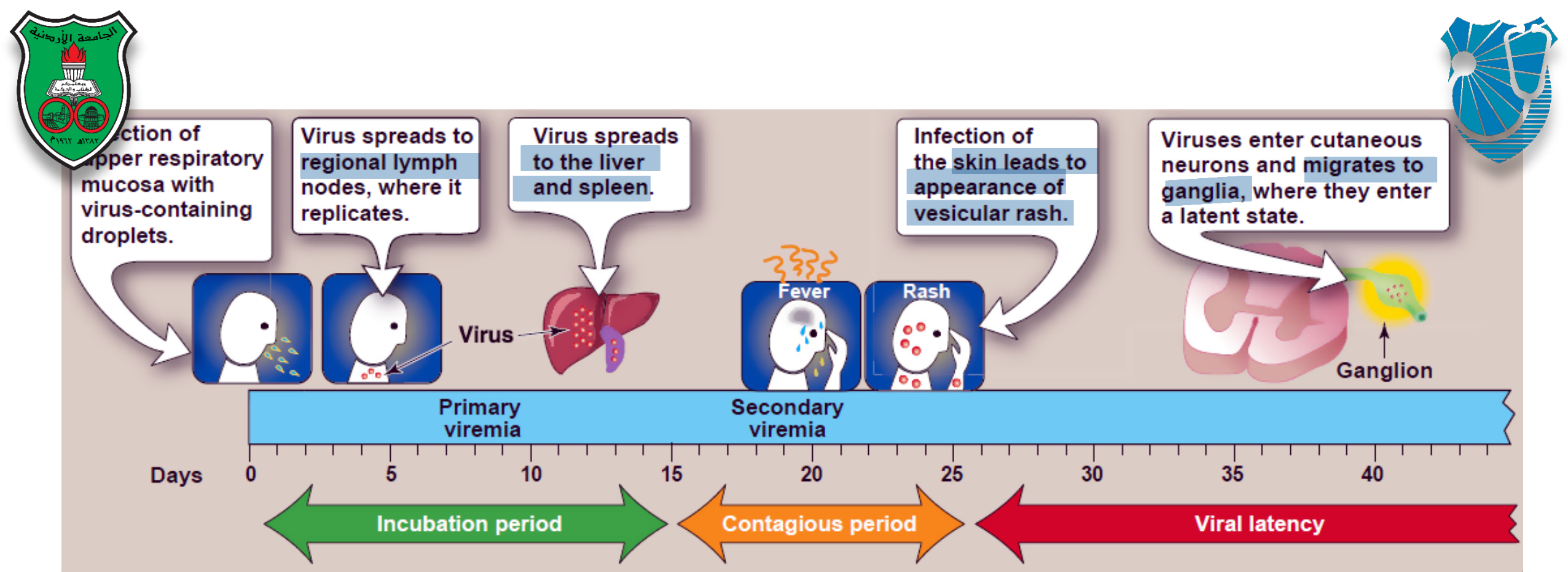
يصير عند:

كبار السن

## Immunocompromised

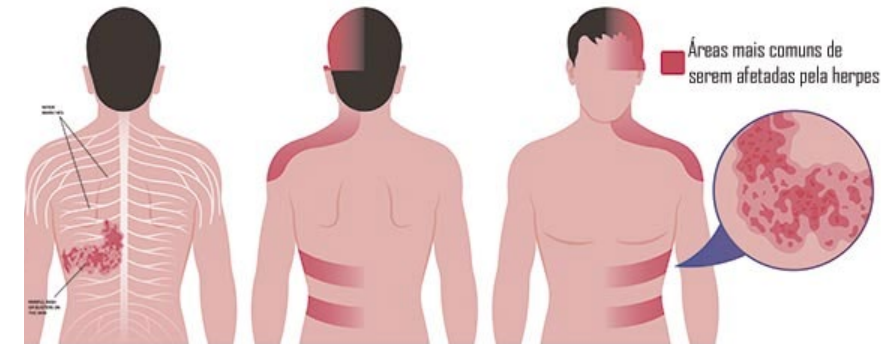
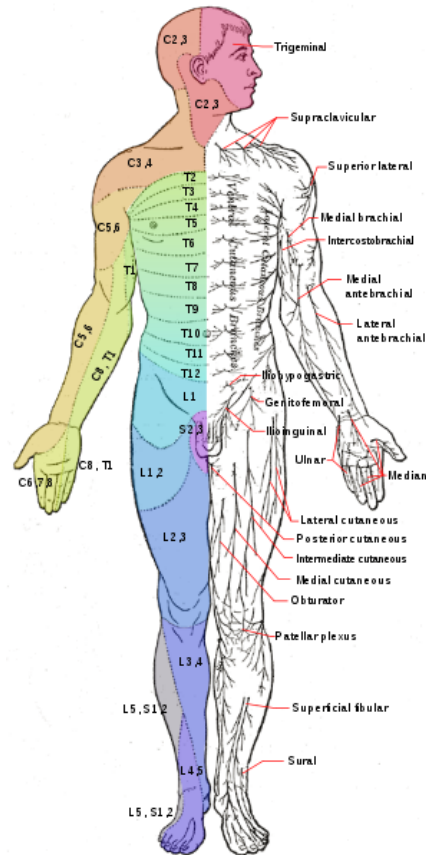
الفيروس يرجع يمشي anterograde على العصب → الجلد

يسبب Dermatome واحد فقط



# VZV Pathogenesis & Pathology



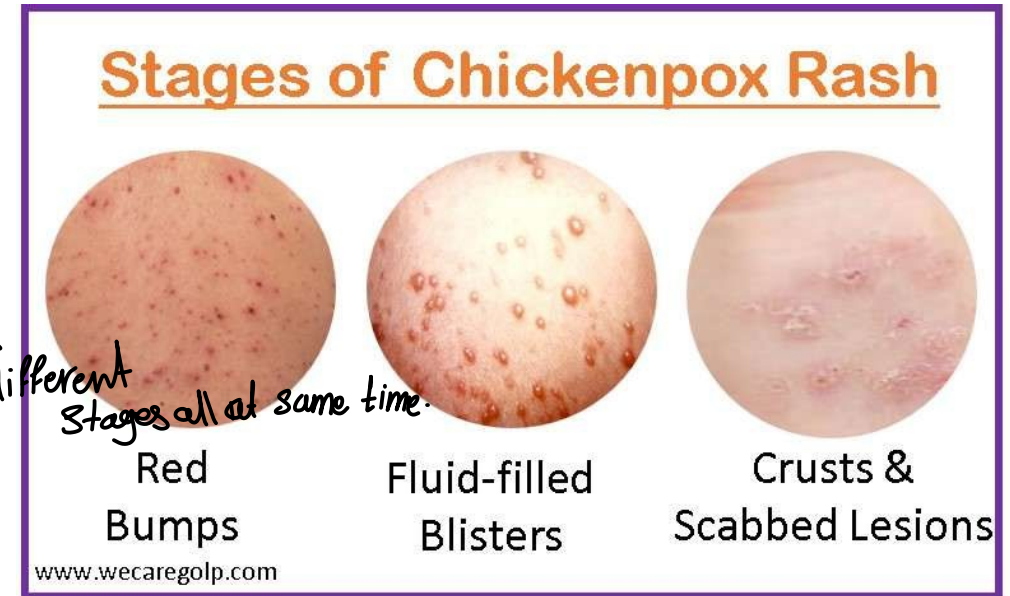


# VZV Pathogenesis & Pathology



# Chickenpox Clinical Features

- Subclinical varicella is unusual. *انه يكون asymptomatic which is very rare.*
- 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. *بداية*
- Successive fresh vesicles appear in crops, so all stages of macules, papules, vesicles, and crusts may be seen at one time. *different stages all at same time.*
- The rash lasts about 5 days.
- Complications are rare in normal children, and the mortality rate is very low.



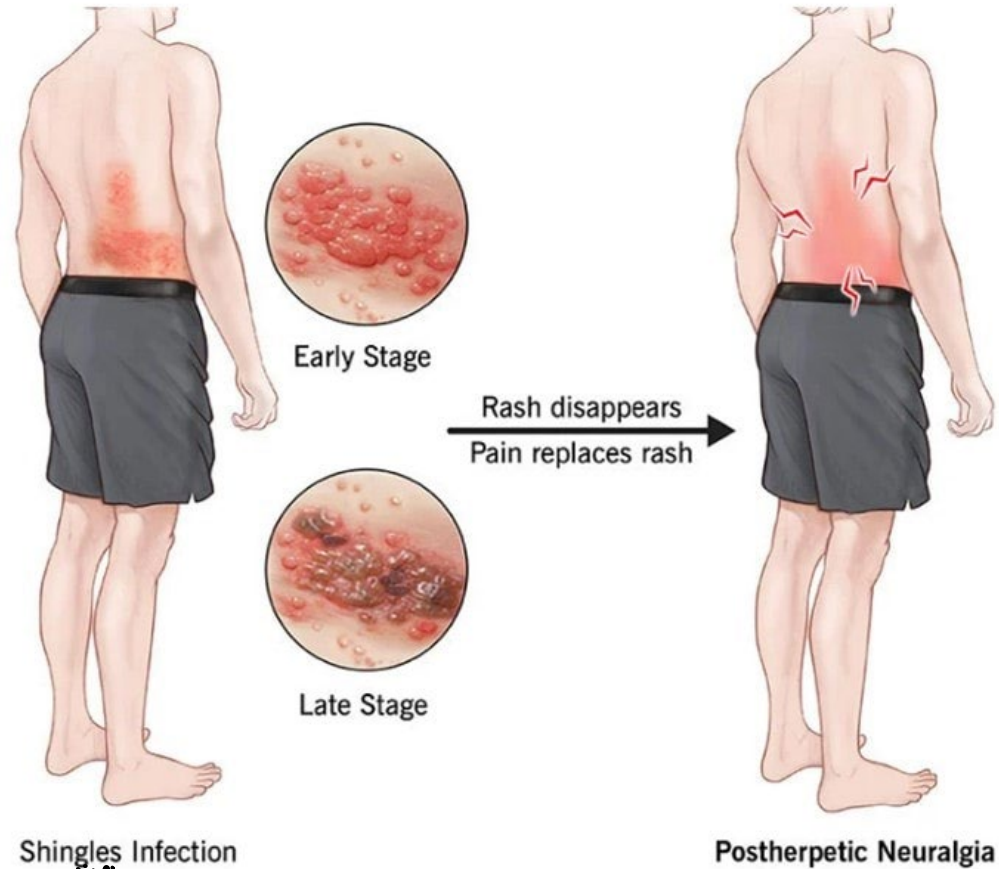
\* in Smallpox the lesions are present as macules & then papules all of the lesions



# Zoster Clinical Features

- Zoster occurs in immunocompromised persons.
- It starts with severe pain in the area of skin or mucosa supplied by the sensory nerves and ganglia.   
*قبل الطفح* (before the rash)   
*reactivation*   
*لـ الى مـ فيها* (to the area where it is)
- 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.   
*Common sites*
- The most common complication of zoster in the elderly is postherpetic neuralgia which is a protracted pain that may continue for months.

## Post Herpetic Neuralgia



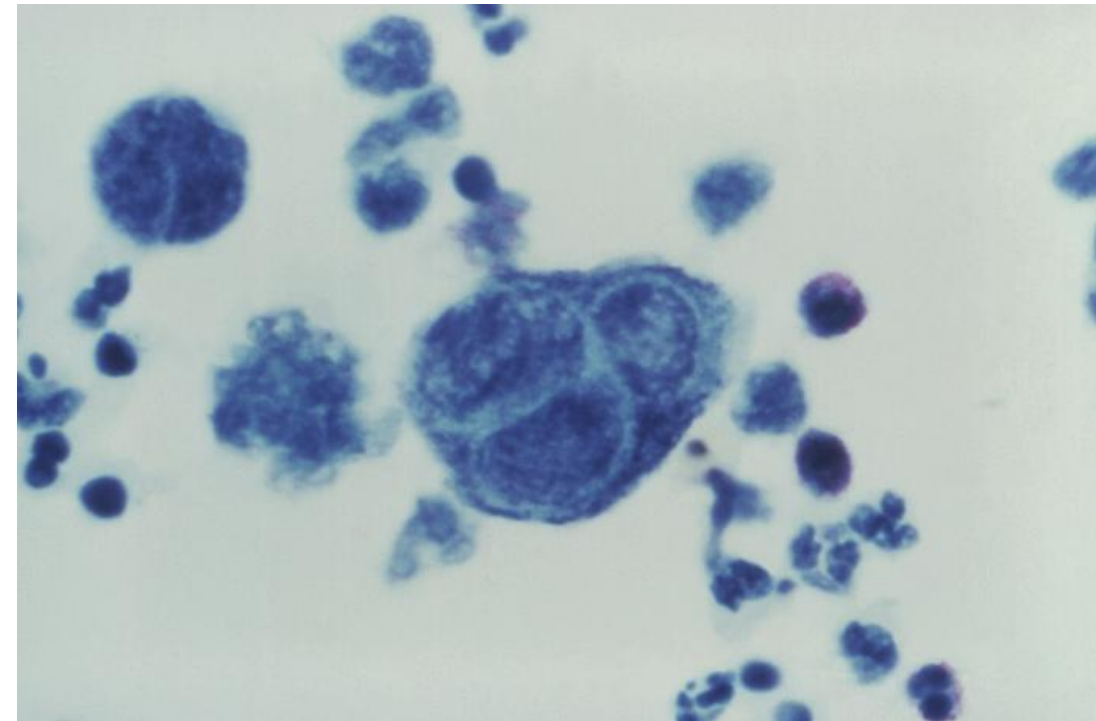
Shingles Infection  
آلم فـ مـ  
nerve pain following  
herpes  
Neurology and Orthopaedic Clinic Singapore





# VZV – Diagnosis, Treatment, and Prevention

- Diagnosis: Clinical, Tzanck smear, Serology, PCR.
- Varicella in normal children is a mild disease and requires no treatment.
- Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults.
- A live attenuated varicella vaccine is highly effective at inducing protection from varicella in children (80–85% effective), but less so in adults (70%).
- Varicella infections can occur in vaccinated persons, but they are usually mild illnesses.
- Zoster vaccine is indicated for prevention of shingles in adults  $\geq 50$  years.





# Epstein-Barr Virus (EBV)

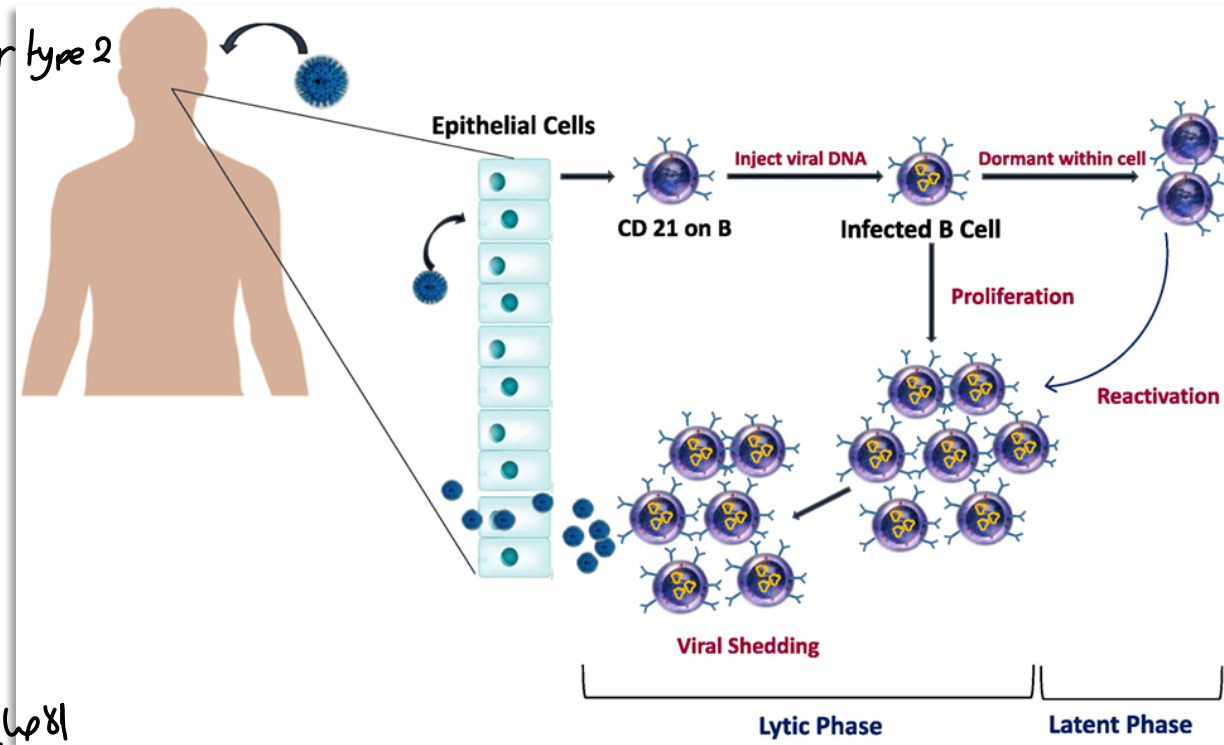
↳ Oncovirus

دسفنزون  
other subfamily  
Which one? Gamma  
Herpesvirus.

تسبب  
development of cancers



- Tropism: B cells, oral epithelial cells.
- Latency: B cells.
- Cellular receptors: CR2 (CD21). *complement receptor type 2*
- Transmission: Contact with oropharyngeal secretions, saliva.
- In developing countries, infections occur early in life; more than 90% of children are infected by age 6. *كلما كان العمر أقل احتمالاً ظهور الأعراض بتكون أقل*  
*asymptomatic*
- These infections in early childhood usually occur without any recognizable disease.
- The inapparent infections result in permanent immunity to infectious mononucleosis. *الاصابة المبكرة غير ظاهرة بتعطي مناعة دائمة ضد*





# Infectious Mononucleosis (IM)

The incubation period for IM is about 4 to 6 weeks.

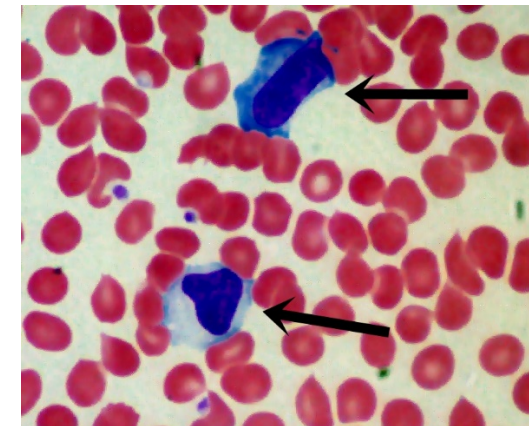
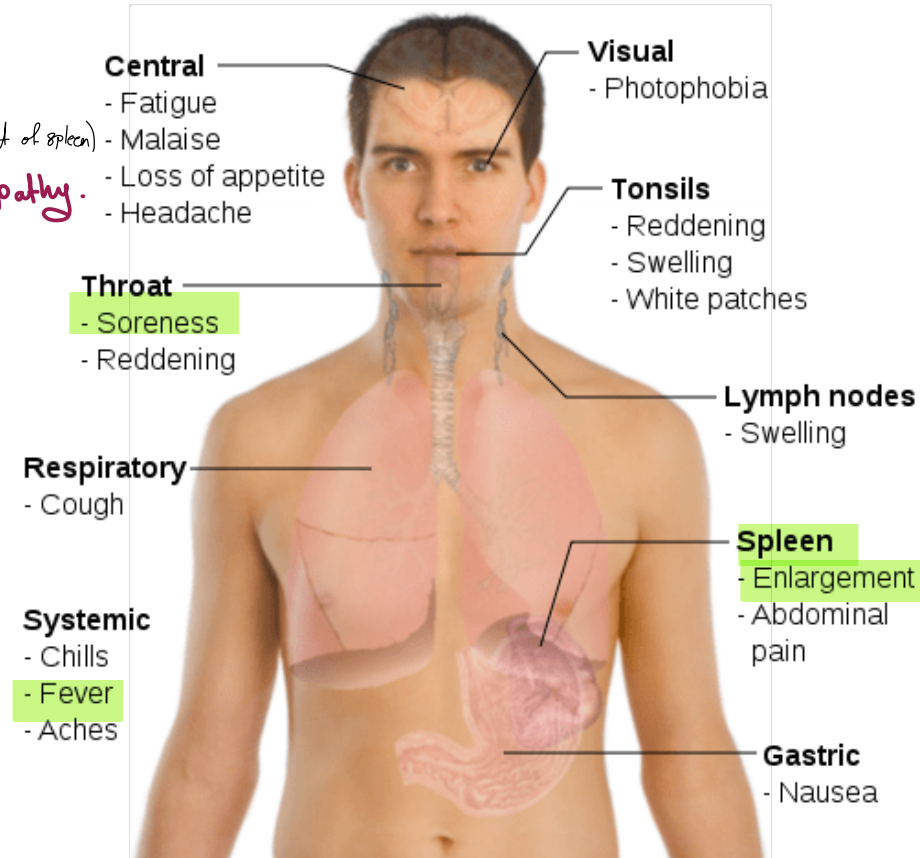
The peripheral blood shows leukocytosis, an increase in T cells but not B cells, and atypical lymphocytes (predominantly activated T cells having large amounts of cytoplasm).

عبارة عن T lymphocytes activated to attack B lymphocytes التي في جهاز EBV  
بالرغم أنه الخلايا الحادة هي B cells

## Clinical Features (The doctor mentioned)

- Fever
- Sore throat
- Fatigue
- Splenomegaly (enlargement of spleen)
- Cervical Lymphadenopathy.

## Main symptoms of Infectious mononucleosis







# Cancers Associated with EBV Latent Gene Expression



من كل الناس التي عندهم EBV يصابوا بـ Cancer

Disease	EBERs	EBNA-1	EBNA-2	LMP-1	LMP-2
<b>Burkitt lymphoma</b>	+	+	-	-	-
<b>Nasopharyngeal carcinoma</b>	+	+	-	+	+
<b>Hodgkin disease</b>	+	+	-	+	+
<b>Peripheral T-cell lymphoma</b>	+	+	-	+	+
<b>Lymphoproliferative disease</b>	+	+	+	+	+

nuclear antigens

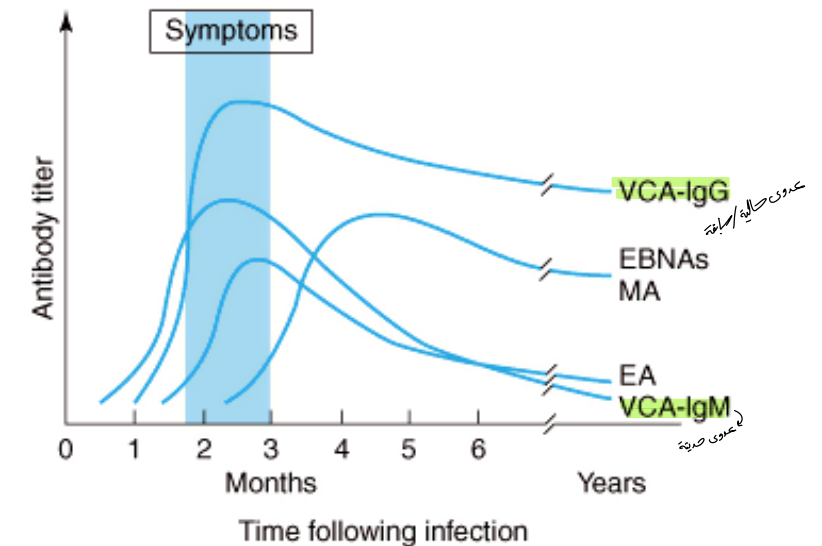
latent membrane proteins

(+) الجين مفعل  
(-) الجين من مفعل  
للنوع الأكثر شيوعاً  
نادر الأورام



## IM Laboratory Diagnosis and Rx

- The diagnosis of IM in patients with typical symptoms is made by a positive heterophile antibody.  
*Antibody هي بروتين ← يمنع انتشار فيروس EBV ← مناعة ضد الفيروس ← EBV للزمن بعد الإصابة بـ IM*
- Titers of EBV-specific antibodies (VCA, EA, MA and EBNA) are measured.  
*Antibodies نوعية ← يقيس مستوى من EBV ← ليعرف لما نقيسهم بنوعه*
- Detection of EBV DNA in the blood can be useful for diagnosis of IM if serologic results are equivocal.  
*PCR ←* *لما نقيسهم بنوعه* *active replication* *هل الـ DNA موجودة؟ ضريبة؟ صافية؟* *غامض*
- Treatment of IM is supportive. Contact sports should be avoided during the acute phase of the disease due to the risk of splenic rupture.





# Cytomegalovirus (CMV)

الفيروس المفضل للخلايا

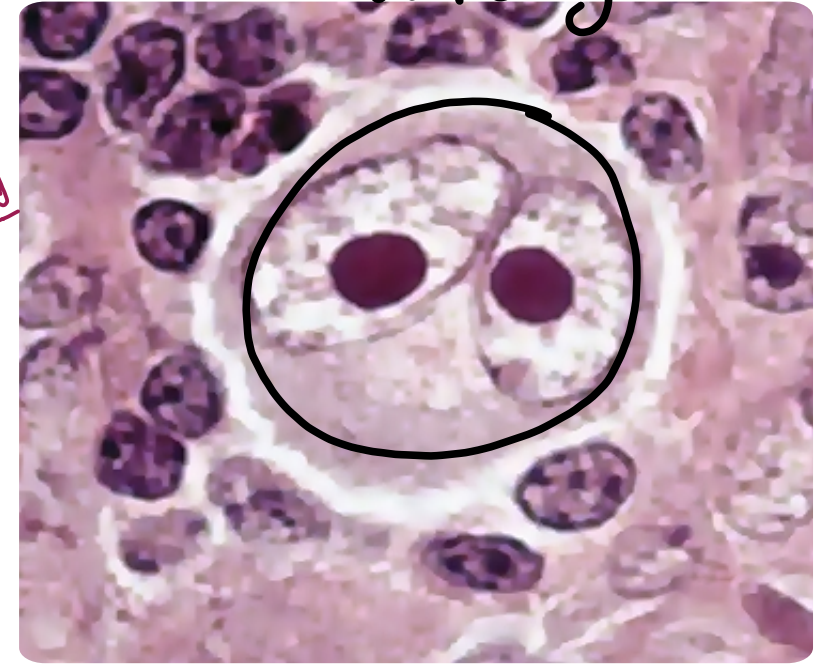
نقر يبيأكل أنواع الخلايا

- Tropism: Epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, parenchymal cells and connective tissue, cells of virtually any organ and various hematopoietic cell types.
- Latency: Myeloid cells.  
*related to bone marrow*
- Transmission: Contact with urine, saliva, congenital, sexual.  
*↳ mother to fetus*
- CMV is the most common congenital viral infection in the developed world, with an overall birth prevalence of approximately 0.6%.
- CMV causes IM-like syndrome in primary infection.  
*IM يسهل*

لكن Negative ← heterophile antibody

الجزء من يصب أي عضو

owl's eye inclusion







# CMV in Immunocompromized Host

## Congenital CMV



- Pneumonia is a frequent complication.
- CMV often causes disseminated disease <sup>مرض منتشر (من مكانه الأصلي إلى أجزاء أخرى في الجسم)</sup> in untreated AIDS patients.
- Gastroenteritis and retinitis are common problems, the latter often leading to progressive blindness.   
*stomach & intestines*   
*eye*
- Approximately 10% of congenitally infected infants have signs and symptoms of disease at birth.
- Symptomatic infants have a high risk for subsequent neurologic complications, including hearing loss, mental retardation, microcephaly, development delay, seizure disorders, and cerebral palsy.
- The cornerstone of antiviral therapy is ganciclovir.   
*الحجر الأساس*   
*دماغ*   
*مخاض*   
*صغير ال*   
*بجرب*   
*Small brain*





# CMV Laboratory Diagnosis

- PCR assays have replaced virus isolation for routine detection of cytomegalovirus infections. Cell culture methods of viral isolation are too slow to guide Rx.   
→ Very slow
- CMV produces a characteristic CPE (Massively enlarged "cytomegalic" cells are typical, besides Owl's eye appearance of inclusion bodies "intranuclear basophilic inclusions").   
→ cytopathic effect.   
الفيروسات التي يجعلها الـ virus بالـ CPE
- Blood and urine are most commonly tested.   
نأخذ العينة
- Serology: Detection of viral IgM antibodies suggests a current infection.

\* تنبغي يضمن بالعدوى الحديثة

→ If it was positive it means

الشخص مصاب حاليًا/ حديثًا

والتي من ذلك  
PCR  
NOTE  
The

Created by Notein



# Roseola viruses

## HHV-6 and HHV-7



- Both HHV-6 and HHV-7 are causative agents of roseola infantum (exanthem subitum), although infection with HHV-7 is more frequently asymptomatic.
- HHV-6 exists in two variants, HHV-6A and HHV-6B.
- Transmission: Respiratory, direct contact.
- Tropism: HHV-6: T cells, B cells, natural killer (NK) cells, Monocytes-macrophages, epithelial cells and nerve cells. HHV-7: CD4+ T lymphocytes and epithelial cells of salivary glands.
- Latency: Peripheral blood mononuclear cells (PBMCs).
- Cellular receptors: HHV-6: CD46. HHV-7: CD4.

Rash  
عن نتوءات  
Small roses.

سبب الحضانة

That's why it's associated with aseptic meningitis in a very small number, that's why the panel of PCR detect the causes of A. meningitis find enterov. HSVs & HHV6  
لانه بعض الحالات  
سبب A. Meningitis

Same receptor for Measles virus



# Exanthem Subitum (Roseola Infantum, Sixth Disease)



درجۃ الحرارة بتكون عالیه جداً، ممكن یعد أنه bacterial inf. أکثر من انه Viral

\* قبل ظهور Rash

- In the classic presentation, an infant develops sudden fever, which lasts for a few days, followed immediately by a rash that appears on the trunk and face and spreads to lower extremities as the fever subsides.
- Due to the high fever, ES might be associated with febrile seizures.
- The disease is nearly always harmless, characterized by sudden onset with high fever and manifests as a typical exanthem in small children.
- Reports of HHV-6-caused illness in adults are rare and the clinical pictures described resemble mononucleosis (EBV-negative mononucleosis).



إصابة بـ  
في:  
Reactivation  
• immunocompromised  
بطلع أعراض خفيفة  
IM-like illness





# Kaposi's Sarcoma-Associated Herpesvirus

Gamma Herpes subfamily.

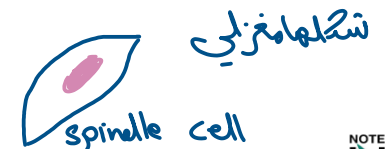
- Tropism: B lymphocytes.
- Latency: B lymphocytes.
- Transmission: Sexual contact, saliva
- Some infections are acquired early in life by nonsexual routes, possibly through contact with oral secretions. / breast milk
- It appears to be sexually transmitted among gay men, who have a higher seroprevalence compared to the general population.
- Kaposi's sarcoma (KS) seems to originate from the viral modified pluripotent mesenchymal cells of the connective tissue transformed in spindle-shaped KS cells.

فيتشابه مع EBV في

في القارة الافريقية

خلايا منة بتقدر تتحول لأكتر من نوع خلية

اللي عندهم AIDS  
عندهم احتمال أكبر  
of developing  
of Kaposi's  
Sarcoma





# Kaposi Sarcoma

في أي منطقة بالجسم : internal organ  
skin , or anywhere else .

- **Nodular lesions of variable colors** affecting the skin, mouth, GI tract or respiratory tract.  
 raised lesion larger than 1cm

- Four classes of KS including:

✓ Classic KS. حول البني الأبيض المتوسط التجاري في السن  
its course is somewhat long so the individual die from it

✓ Endemic or African KS.

✓ Iatrogenic KS associated with immunosuppressive therapies in transplant patients.  
مربطة باستخدام أدوية أو نقل الأعضاء

✓ Epidemic or AIDS-related KS.  
أكثر واهم من قبل

AIDS / HIV



# HHV-8

- **Primary effusion lymphoma (PEL)**, which is an expansion of B cells predominantly in serosal cavities such as the pericardium, pleura, and peritoneum. *lymphoma داخل هذه التجاويف البطن الصدر حول القلب*
- **Multicentric Castleman's disease (MCD)**. MCD is a rare, polyclonal, lymphoproliferative disease that can develop in both HIV-negative and HIV-positive individuals. *أكثر من مركزية (مع مثاقولاه معدي)*
- KS incidence is 1 in 100,000 in the general population, whereas in HIV-infected individuals, the incidence is around 1 in 20. *→ rate in general population. ضعف المناعة = خطر عالي لـ KS*
- Diagnostic confirmation of KS is done through **histopathology**.
- Confirmation is done by immunohistochemistry in tissues using monoclonal antibodies to the KSHV. *if positive means the diagnosis is confirmed*
- Rx: **HAART** can induce AIDS-KS regression. Isolated lesions are treated with radiotherapy. Systemic chemotherapy is useful for the treatment of disseminated disease. *الحد 2*



Virus	Disease(s)	Transmission	Tropism (Target cells)	Latency	Key Clinical Features	Diagnosis	Treatment / Prevention
Varicella Zoster Virus (VZV)	Chickenpox (primary), Zoster/Shingles (reactivation)	Respiratory, direct contact	Epithelial cells	Sensory (dorsal root) ganglia	Chickenpox: generalized vesicular rash (different stages) • Zoster: painful dermatomal rash, post-herpetic neuralgia	Clinical, PCR, Tzanck	Acyclovir (adults, immunocompromised) • Varicella & Zoster vaccines
Epstein-Barr Virus (EBV)	Infectious mononucleosis, lymphomas, NPC	Saliva	B cells, oral epithelium	B cells	IM triad: fever, pharyngitis, posterior cervical lymphadenopathy • Splenomegaly	Heterophile Ab (Monospot), EBV Abs, PCR	Supportive only • Avoid contact sports
Cytomegalovirus (CMV)	Congenital CMV, IM-like illness, severe disease in immunocompromised	Urine, saliva, sexual, congenital	Almost any cell	Myeloid cells	Congenital: hearing loss, microcephaly • AIDS: retinitis, pneumonia, GI disease	PCR, Owl's eye inclusions, IgM	Ganciclovir
HHV-6	Roseola infantum (sixth disease)	Respiratory, contact	T, B, NK cells, monocytes, epithelial, nerve cells	PBMCs	High fever → fever subsides → rash • Febrile seizures	Usually clinical	Supportive
HHV-7	Roseola (often asymptomatic)	Respiratory, contact	CD4+ T cells, salivary glands	PBMCs	Similar to HHV-6 but milder / asymptomatic	Usually clinical	Supportive
Kaposi's Sarcoma-Associated Herpesvirus (HHV-8)	Kaposi sarcoma, PEL, Castleman disease	Sexual, saliva	B lymphocytes	B lymphocytes	KS: purple nodular lesions (skin, oral, GI) • ↑ risk in HIV	Histopathology + IHC	HAART, radiotherapy, chemotherapy





**Thank You...**  
**Wishing you all the best!**

