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Viral Infections Causing Skin Lesions 

Introduction

- Herpes simplex virus (HSV-1 & HSV-2) and varicella-zoster virus (VZV) → Vesicles
- Human herpesvirus 8 (HHV-8) → Kaposi's sarcoma (purple macular or nodular lesions)
- Smallpox virus → Pustules (eradicated)
- Molluscum contagiosum virus → Fleshy papules with umbilicated centers
- Human papillomavirus (HPV) → Papillomas (warts) on skin/mucous membranes like cervix & larynx
- Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) → Do not cause skin lesions

🔑 Exam tip: Remember: "Only CMV and EBV skip the skin"

DNA Viruses of the Skin

All these viruses have DNA genomes:

Virus Family	Genome Type	Replication Site
Herpesviruses	Linear dsDNA	Nucleus
Poxviruses	Linear dsDNA	Cytoplasm
Human Papillomavirus	Circular dsDNA	Nucleus

🧠 Note: Poxviruses are unique as they replicate in the cytoplasm, unlike other DNA viruses.

Features of Skin Lesions ✳

Virus	Typical Skin Lesion
HSV-1	Vesicle
HSV-2	Vesicle
VZV	Vesicle

CMV	None
EBV	None
HHV-8	Flat or nodular purple lesion
Smallpox virus	Pustule
Molluscum contagiosum virus	Fleshy papule with umbilicated center
HPV	Papule with rough, spiny, cauliflower-like projections

Viral Properties

Property	Herpesviruses	Poxviruses	Human Papillomavirus
Virus family	Herpesviruses	Poxviruses	Papillomaviruses
Genome	dsDNA; linear	dsDNA; linear	dsDNA; circular
Virion DNA	No	No	No

polymerase			
Virion RNA polymerase	No	Yes	No
Nucleocapsid	Icosahedral	Complex	Icosahedral
Envelope	Yes	Yes	No

🔑 Memory tip: Poxviruses are the only DNA virus with cytoplasmic replication and its own RNA polymerase.

Common Herpesvirus Infections 🔁

Virus	Primary Infection	Usual Latency Site	Recurrent Infection	Transmission
HSV-1	Gingivostomatitis	Cranial sensory ganglia	Herpes labialis, encephalitis, keratitis	Respiratory secretions, saliva
HSV-2	Herpes genitalis, perinatal disseminated disease	Lumbar/sacral sensory ganglia	Herpes genitalis	Sexual contact, perinatal infection
VZV	Varicella	Cranial/thoracic sensory ganglia	Zoster	Respiratory secretions

EBV	Infectious mononucleosis	B lymphocytes	Asymptomatic shedding	Respiratory secretions, saliva
CMV	Congenital infection, mononucleosis	Monocytes	Asymptomatic shedding	Intrauterine, transfusions, sexual contact, secretions
HHV-8	Uncertain	Uncertain	Kaposi's sarcoma	Sexual contact, organ transplantation

Flowchart: Herpesvirus Infection Lifecycle 🔄

Primary Infection → Virus enters via mucosa/skin

↓

Replication in epithelial cells → Vesicle formation

↓

Virus spreads to sensory ganglia → Latency established

↓

Trigger (stress, immunosuppression) → Reactivation

↓

Recurrent lesions (labialis/genitalis/zoster)

✅ Quick Exam Points

- Vesicles → HSV-1, HSV-2, VZV
- Purple lesions → HHV-8
- Fleshy papules → Molluscum contagiosum
- Pustules → Smallpox (eradicated)
- Papillomas → HPV
- Cytoplasmic replication → Poxvirus
- Only CMV & EBV → No skin lesions

Herpesviruses 

Overview

The herpesvirus family includes six important human pathogens:

- HSV-1 & HSV-2 (Herpes Simplex Virus)
- Varicella-Zoster Virus (VZV)

- Cytomegalovirus (CMV)
- Epstein-Barr Virus (EBV)
- Human Herpesvirus 8 (HHV-8, Kaposi's sarcoma-associated herpesvirus)

Key Structural Features ◈

- Shape: Icosahedral nucleocapsid
- Envelope: Lipoprotein envelope
- Genome: Linear double-stranded DNA (dsDNA)
- Size: Large, 120-200 nm (second only to poxviruses)
- Polymerase: Virion does not contain DNA polymerase
- Tegument: Protein layer between nucleocapsid and envelope containing regulatory proteins (transcription & translation factors)

🧠 Exam tip: Tegument proteins help the virus replicate efficiently once inside the host cell.

Replication Features:

- Takes place in the nucleus
- Forms intranuclear inclusions
- Envelope is acquired by budding from the nuclear membrane

Latency:

- Herpesviruses establish lifelong latent infections
- After acute infection → virus enters quiescent state in specific cells
- Reactivation occurs with immunosuppression or triggers like:
    - Sunlight 🌞
    - Fever 🤒
    - Stress 😰

Mechanisms of Latency:

- HSV: Latency-associated transcripts (LATS, noncoding

RNAs) suppress viral replication

- CMV: Produces microRNAs and proteins that inhibit apoptosis → infected cells survive

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Clinical Features 

Virus	Primary Infection	Skin Lesions	Reactivation
HSV-1	Gingivostomatitis	Vesicular rash	Herpes labialis
HSV-2	Herpes genitalis	Vesicular rash	Herpes genitalis
VZV	Varicella	Vesicular rash	Shingles (Zoster)
CMV	Usually asymptomatic; congenital infection	None	Asymptomatic shedding
EBV	Infectious mononucleosis	None	Asymptomatic shedding
HHV-8	Often asymptomatic	Purple lesions (Kaposi's sarcoma)	Kaposi's sarcoma

🔑 Exam tip: Alpha herpesviruses → vesicles; Beta & Gamma → may not cause skin lesions.

Histopathology 🔬

- Multinucleated giant cells are seen in:
  - HSV-1 & HSV-2
  - VZV
  - CMV
- Detected by Tzanck smear (painful genital vesicles in HSV-2)

Classification of Herpesviruses 🗂️

Subfamily	Viruses	Target Cells	Latency Site
Alpha	HSV-1, HSV-2, VZV	Epithelial cells	Neurons
Beta	CMV, HHV-6	Various tissues	Monocytes, other Tissues
Gamma	EBV, HHV-8	Lymphoid cells	B lymphocytes or endothelial cells

🧠 Memory tip:

- Alpha = fast replicating → vesicles
- Beta = slow replicating → chronic/subclinical
- Gamma = lymphoid → oncogenic potential

Oncogenic Potential 🎗

- EBV: Burkitt's lymphoma, nasopharyngeal carcinoma
- HHV-8: Kaposi's sarcoma
- Some herpesviruses cause cancer in animals (e.g., leukemia in monkeys, lymphomatosis in chickens)

Flowchart: Herpesvirus Lifecycle & Latency 🔄

Primary Infection → Virus enters mucosa/skin

↓

Replication in epithelial cells → Vesicle formation

↓

Virus spreads to latency site → Neurons (alpha), Monocytes (beta), Lymphoid cells (gamma)

↓

Latency maintained (LATS or miRNAs inhibit replication)

↓

Trigger (stress, fever, UV light) → Reactivation

↓

Recurrent infection → Symptoms similar or different depending on virus

☑ Quick Exam Tips

- Vesicular rashes: HSV-1, HSV-2, VZV
- No rash: CMV, EBV
- Multinucleated giant cells: HSV-1, HSV-2, VZV, CMV
- Oncogenic: EBV, HHV-8
- Latency site: Alpha → neurons, Beta → monocytes, Gamma → lymphoid

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Herpes Simplex Viruses (HSV-1 & HSV-2)

Overview

HSV-1 and HSV-2 are distinguished by:

1. Antigenicity (glycoprotein G differences)

2. Location of lesions

    - HSV-1 → Above the waist (face, mouth)
    - HSV-2 → Below the waist (genitals)

🧠 Exam tip: HSV-1 → oral & facial, HSV-2 → genital, but oral-genital transmission can mix them (~10–20% cases).

Clinical Features 

Feature	HSV-1	HSV-2
Primary Disease	Gingivostomatitis, keratoconjunctivitis, encephalitis	Herpes genitalis, neonatal herpes, aseptic meningitis
Recurrent Infection	Herpes labialis (cold sores)	Herpes genitalis

Neonatal Disease	Rare	Skin lesions, encephalitis, disseminated infection
Dissemination in Immuno-compromised	Yes	Rare
Skin Lesions	Vesicles above the waist	Vesicles below the waist (genitals)
Giant Cells	Yes	Yes
Lab Diagnosis	PCR, culture, Tzanck smear	PCR, culture, Tzanck smear
Antiviral Therapy	Acyclovir	Acyclovir
Vaccine	None	None

🔑 Quick tip: Both HSV-1 & HSV-2 cause multinucleated giant cells, seen in Tzanck smears.

Important Properties 🧬

- Structurally indistinguishable, both with:

- Icosahedral nucleocapsid
- Lipid envelope
- Linear dsDNA genome

- Can be differentiated using:

  - Restriction endonuclease patterns of DNA
  - Type-specific monoclonal antisera against glycoprotein G

- Humans are the natural hosts

Replication Cycle 🔄

Stepwise Summary:

1. Attachment & Entry

   HSV binds heparan sulfate → nectin receptor
   ↓
   Fusion of viral envelope with cell membrane → release of nucleocapsid + tegument proteins

2. Transport to Nucleus

Nucleocapsid moves to nuclear pore

↓

Viral DNA enters nucleus + VP16 protein

↓

Genome DNA circularizes

3. Immediate Early (IE) Protein Synthesis

VP16 activates transcription of IE genes

↓

IE proteins regulate early protein synthesis

4. Early Protein Synthesis

- DNA polymerase → genome replication
- Thymidine kinase → target for acyclovir

5. Late Protein Synthesis

- Structural proteins → transported to nucleus
- Virion assembly occurs
- Envelope acquired by budding through nuclear membrane
- Virion exits via tubules/vacuoles

6. Latency

- Circular HSV DNA resides in neurons
- Limited transcription → latency-associated transcripts (LATS)
- Reactivation occurs when LATS regulation is removed

Flowchart: HSV Replication & Latency ◈

Attachment → Fusion & entry → Nucleocapsid transport → Nuclear docking

↓

Circularization of genome → IE gene transcription → IE proteins

↓

Early protein synthesis → DNA replication

↓

Late protein synthesis → Assembly → Budding → Exit

↓

Latency in neurons → LATS expressed → Reactivation possible

Transmission & Epidemiology 🌍

- HSV-1: Saliva → mainly oral/facial infections
- HSV-2: Sexual contact → mainly genital infections
- Oral-genital transmission possible (~10-20%)
- Asymptomatic shedding contributes significantly to transmission
- Epidemiology:
    - HSV-1: ~80% infected, most primary infections in childhood
    - HSV-2: 40% have recurrent genital herpes, seroconversion occurs with sexual activity

✅ Key Exam Points

- HSV-1 → oral, above waist; HSV-2 → genital, below waist

- Multinucleated giant cells → Tzanck smear
- Early proteins → DNA polymerase & thymidine kinase → target for acyclovir
- Latency → LATS in neurons suppress replication
- Transmission → HSV-1 saliva, HSV-2 sexual, but asymptomatic shedding exists

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Herpes Simplex Virus (HSV) – Pathogenesis & Immunity 

Pathogenesis 

1. Entry & Initial Replication

- Virus replicates in skin or mucous membrane at site of infection
- Migrates retrograde along neurons → establishes latency in sensory ganglia

    - HSV-1 → Trigeminal ganglia
    - HSV-2 → Lumbar & sacral ganglia

2. Latency 💤

    - Viral DNA mostly in cytoplasm, not integrated into host DNA

    - Latency-associated transcripts (LATS) suppress viral replication

    - Reactivation triggered by:

        - Sunlight ☀️
        - Hormonal changes
        - Trauma
        - Stress 😰
        - Fever 🤒

3. Reactivation 🔄

    - Virus migrates anterograde along neuron

    - Replicates in skin → vesicular lesions

- Vesicles contain virus particles + cell debris → can infect others

Skin Lesion Progression 🩹

Erythema → Papules → Vesicles → Ulcers → Crusts

- Prodrome: itching or tingling at site
- HSV-2 → more frequent recurrences than HSV-1
- Multinucleated giant cells at base of lesions

Immunity 🛡️

Immunity Type	Role in HSV Infection
Type-specific humoral immunity	Provides partial protection; HSV-1 antibodies can reduce severity of HSV-2 infection, but do not prevent reinfection
Cell-mediated immunity (CMI)	Crucial for controlling viral replication; reduced CMI → reactivation, severe disease

🧠 Exam tip: CMI is more important than antibodies for controlling HSV.

Diseases of HSV-1 and HSV-2 

Disease	Age Group / Risk	Key Features
Gingivostomatitis	Children	Fever, irritability, vesicles in oral cavity; heals in 2–3 weeks
Herpes labialis (cold sores)	Adults	Recurrent vesicles at lip/nose mucocutaneous junction; frequent recurrences at same site
Kerato conjunctivitis	Adults	Corneal ulcers, conjunctival lesions; recurrent infections → scarring & blindness
Encephalitis	Adults	Temporal lobe necrosis; fever, headache, vomiting, seizures, altered mental status; high mortality
Herpetic whitlow	Medical personnel	Pustular lesions on fingers/hands from contact with HSV lesions
Herpes gladiatorum	Wrestlers / close-contact athletes	Vesicular lesions on head, neck, trunk
Eczema herpeticum	Children with atopic dermatitis	Vesicles at eczema sites

Disseminated infections	Immuno compromised patients	Esophagitis, pneumonia, severe systemic disease
Genital herpes	Adults via oral-genital contact	Vesicular genital lesions (HSV-1)

🔑 Exam tip: HSV-1 primary infection is more severe than recurrences; lesions heal spontaneously.

Flowchart: HSV-1 Pathogenesis & Lesion Formation

🔁

Initial Infection (skin/mucosa) → Virus replicates locally

↓

Retrograde transport along neurons → Latency in sensory ganglia

↓

Latency maintained (LATS expressed)

↓

Trigger (stress, UV, fever) → Reactivation

↓

Anterograde transport → Replication in skin/mucosa

↓

Vesicle formation → Virus released → Transmission

✅ Key Exam Points – HSV-1

- Latency site: Trigeminal ganglia
- Common lesions: Oral vesicles, keratoconjunctivitis, encephalitis
- Giant cells: Seen at base of vesicles (Tzanck smear)
- Triggers of reactivation: Sunlight, stress, trauma, fever
- Immunity: CMI is essential; humoral immunity provides partial cross-protection

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Clinical Manifestations of HSV-1 and HSV-2

1 Primary & Recurrent Diseases

(I) Genital Herpes (Herpes Genitalis)

- Lesions: Painful vesicular eruptions on ♂ genitals, ♀

genitals, and anal region

- Primary infection:
    - More severe & prolonged than recurrences
    - Often accompanied by fever 🌡 and inguinal lymphadenopathy
- Asymptomatic infections:
    - Common — many have antibodies without disease
    - Virus may shed intermittently → source of transmission
    - In men → latent in prostate/urethra
    - In women → latent in cervix

Causative Ratios

- HSV-2: 80–90 % of genital herpes cases
- HSV-1: 10–20 % (oral-genital transmission)

Recurrence Patterns 🔁

Virus Type	Recurrence Frequency	Clinical Notes
HSV-2	~70 % within 1 year; avg 4–5	More frequent &

	episodes/year	symptomatic
HSV-1	~1 episode/year	Usually milder

💡 *Clinical significance:* HSV-2 lesions warrant suppressive antiviral therapy (e.g., acyclovir) due to frequent recurrence.

2 Neonatal Herpes 👶

Source & Transmission

- Usually from mother's vesicular lesions during birth
- Can also occur with asymptomatic viral shedding in birth canal
- Highest risk:
    - Primary maternal HSV-2 infection in third trimester
    - Because → no protective maternal IgG yet

Forms of Neonatal Disease

Type	Severity	Description
Disseminated	Severe	Multi-organ involvement; encephalitis;

		high mortality
Localized (SEM)	Mild–moderate	Skin, eye, mouth lesions
Asymptomatic	Mild	Virus detectable, no clinical lesions

Key Prevention Measures

- Cesarean section if active lesions or positive cultures during labor
- Maternal antibodies (IgG) from prior infection → cross placenta → protective effect 💧
- Both HSV-1 & HSV-2 can cause neonatal infection after birth from infected handlers
- ❌ *Do not cause congenital malformations* to any significant extent

3 Aseptic Meningitis 🧠

- Caused by HSV-2
- Typically mild & self-limited

- Few long-term neurological sequelae

4 Erythema Multiforme 🎯

Overview

- Immune-mediated skin reaction to HSV antigens
- Appears after HSV-1 or HSV-2 infection

Clinical Features

- Target ("bull's-eye") lesions 🎯
    - Central red area → surrounded by pale zone → outer red ring
- Distribution: Symmetrical on trunk, hands, feet
- Form: Macules or papules
- Acyclovir helps prevent recurrence by lowering antigen exposure

Other Causes

- Drugs: Sulfonamides, anticonvulsants, etc. 💊

- Infections:
    - *Mycoplasma pneumoniae*
    - *Hepatitis B & C viruses*

5 Erythema Multiforme Major (Stevens-Johnson Syndrome) ⚠

- Severe form of erythema multiforme
- Features:
    - Fever 🧒 🌡
    - Erosive oral lesions
    - Extensive skin desquamation
- Most common infectious cause: *Mycoplasma pneumoniae*

Flowchart - HSV-2 Pathogenesis & Transmission 🔄

Initial infection during sexual contact

↓

Virus replicates in genital epithelium

↓

Retrograde transport → sacral or lumbar ganglia (latency)

↓

Trigger (stress, hormones, trauma, fever) → reactivation

↓

Anterograde transport → vesicular genital lesions

↓

Virus shed → sexual / perinatal transmission

↓

If pregnant mother infected →

Primary infection → high viral load, no IgG → neonatal infection

Recurrent infection → low viral load, maternal IgG → protection

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Summary Table for HSV-1 and HSV-2

Feature	HSV-1	HSV-2
Primary site	Oral mucosa / lips (causing cold sores)	Genital mucosa / anal area
Latency site	Trigeminal ganglia	Lumbar & sacral ganglia
Common recurrences	Oral / labial vesicles ("cold sores")	Genital vesicles
Key complication	Encephalitis (especially temporal lobe)	Neonatal herpes
Neurological disease	Encephalitis	Aseptic meningitis
Immunologic reaction	Erythema multiforme	Erythema multiforme
Prevention in neonates	Avoid direct contact with active oral lesions (e.g., kissing newborn)	Cesarean section if active genital lesions
Protection	Maternal IgG gives partial protection if recurrent infection	Maternal IgG in recurrent infection provides protection

🔬 Laboratory Diagnosis of HSV-1 & HSV-2

Test / Method	Principle / Description	Usefulness	Notes / Key Points
PCR (Polymerase Chain Reaction)	Detects HSV DNA directly from lesion or CSF	☆ Most rapid & sensitive	Can distinguish HSV-1 vs HSV-2 easily
Viral Culture	Virus grown → observe cytopathic effect (CPE) in 1-3 days	Standard method (though slower)	Confirm identity via fluorescent antibody staining or ELISA detecting viral glycoproteins
Monoclonal antibody test (ELISA)	Detects glycoprotein G specific to HSV-1 or HSV-2	Differentiates HSV-1 vs HSV-2	Commonly used in labs for typing
Tzanck Smear	Giemsa stain from vesicle base → multinucleated giant cells	Rapid presumptive diagnosis	Indicates herpesvirus infection, but not type-specific
Direct Fluorescent Antibody (DFA) test	Detects HSV antigen in vesicular fluid	Rapid confirmation	Often used when viral load is high

CSF PCR	Detects HSV DNA in cerebrospinal fluid	For herpes encephalitis diagnosis	Fast and reliable
Serology (Neutralization Test)	Detects rise in antibody titer	Useful for primary infection only	✕ Not useful for recurrent infections (antibodies already present)
Neonatal Infection Diagnosis	Culture or PCR from infant specimens	Confirms perinatal HSV	Vital for early treatment

⚠ Remember: PCR is preferred over culture due to speed, sensitivity, and typing accuracy.

💊 Treatment of HSV Infections

Drug / Class	Use / Indication	Mechanism / Notes
Acyclovir (Zovirax)	◈ HSV-1 encephalitis ◈ Primary & recurrent genital herpes ◈ Neonatal HSV-2 infection	Inhibits viral DNA polymerase after activation by viral thymidine kinase
Valacyclovir (Valtrex)	Suppression of genital herpes recurrences	Oral prodrug of acyclovir — better absorption

Famciclovir (Famvir)	Same as above	Oral prodrug of penciclovir
Penciclovir (Denavir)	Recurrent orolabial herpes (HSV-1)	Topical; derivative of acyclovir
Docosanol	HSV-1 cold sores (topical)	Long-chain alcohol; prevents viral entry
Trifluridine (Viroptic)	HSV-1 keratitis (eye infection)	Used topically on cornea
Foscarnet	For acyclovir-resistant HSV strains	Inhibits viral DNA polymerase directly; no activation needed

🧠 Key Concept:

- Antivirals shorten lesions and reduce viral shedding.
- They do not eliminate latency or prevent establishment of latent infection.
- Long-term suppressive therapy (acyclovir/valacyclovir/famciclovir) → reduces recurrence and transmission risk.

🛡️ Prevention of HSV Infections

1 Chemoprophylaxis

- Valacyclovir > Famciclovir for suppressing HSV-2

recurrent genital lesions

- Reduces:
    - Frequency of lesions
    - Asymptomatic viral shedding
    - Transmission to sexual partners

2 Obstetric Measures

- Cesarean section for:
    - Women at term with active genital lesions
    - Positive viral culture from birth canal
- Prevents neonatal HSV transmission

3 Behavioral & Physical Barriers

- Avoid direct contact with active lesions or ulcers ⃠
- Use condoms consistently
- Circumcision reduces risk of acquiring HSV-2 infection

4 Vaccine Status

- ❌ No vaccine currently available for HSV-1 or HSV-2

🌿 Summary Table

Aspect	HSV-1	HSV-2
Preferred diagnostic test	PCR / Tzanck smear	PCR / Culture / ELISA
Most effective treatment	Acyclovir (encephalitis, systemic)	Acyclovir, Valacyclovir, Famciclovir
Resistant strains	Foscarnet-sensitive	Foscarnet-sensitive
Eye infection Treatment	Trifluridine, topical acyclovir	Rare
Neonatal Disease	Rare, postnatal infection	Common during birth
Preventive strategy	Avoid oral contact when active	Cesarean, antivirals, condoms
Vaccine	❌ None	❌ None

 Varicella-Zoster Virus (VZV)

💧 Diseases Caused

- Primary infection: *Varicella (Chickenpox)* 🐥
- *Reactivation (Recurrent form): Zoster (Shingles)* 🗲
- Both are caused by the same virus.
- Humans are the only natural hosts.

🧬 Important Properties

- Belongs to the Herpesviridae family.
- Structurally & morphologically similar to HSV, but antigenically distinct.
- Single serotype.
- Causes both primary (varicella) and recurrent (zoster) diseases.

🔁 Summary of Replicative Cycle

- Similar to Herpes Simplex Virus (HSV).
- VZV undergoes latent infection in sensory ganglia after primary infection.

Transmission & Epidemiology

- Modes of transmission:
    - Respiratory droplets
    - Direct contact with vesicular lesions
- Highly contagious—most infections occur in childhood.
- >90% of people develop antibodies by age 10 (in developed countries).
- Global distribution.
- Before vaccination (pre-2001): Varicella was the most common notifiable disease in the U.S.
- Vaccination has drastically reduced incidence.
- Zoster vesicles contain infectious virus → may cause chickenpox in non-immune children upon contact.
- Hospital risk: Major infection-control concern—can cause disseminated, life-threatening infection in immunocompromised patients.

🧠 Pathogenesis & Immunity

❖ Flowchart:

Inhalation of virus → Infection of upper respiratory mucosa → Viremia (spread via blood) → Replication in skin → Vesicular rash (chickenpox) → Infection of sensory neurons → Retrograde transport to dorsal root ganglia → Latency established

◈ Histopathology: Multinucleated giant cells with intranuclear inclusions in lesions.

◈ During latency:

- Viral DNA remains in nucleus (not integrated into host DNA).

◈ Reactivation (Zoster):

- Triggered by age-related decline in immunity, stress, or local trauma → Vesicular rash along sensory nerve

→ Severe nerve pain (postherpetic neuralgia).

◈ Immunity:

- Lifelong immunity after varicella.
- Zoster can occur once despite immunity to varicella.
- Frequency increases with age due to waning cell-mediated immunity.

🩺 Clinical Findings

🌼 Varicella (Chickenpox)

- Incubation period: 14–21 days
- Prodromal symptoms: Mild fever, malaise
- Rash characteristics:
  - Appears in *crops* on trunk → spreads to face & limbs
  - Lesions in *different stages*: papules → vesicles →

pustules → crusts
    - Pruritus (itching) prominent 🩹

- Severity:
    - Mild in children
    - More severe in adults

- Complications:
    - Varicella pneumonia
    - Encephalitis 🧠
    - Reye's syndrome (when aspirin is given to children):
        - Encephalopathy + hepatic degeneration
        - Associated also with Influenza B virus

⚡ Zoster (Shingles)

- Reactivation of latent VZV in dorsal root ganglia.

- Painful vesicular rash along *dermatomal distribution* of a sensory nerve (commonly on trunk or face).

- Postherpetic neuralgia (PHN): Persistent nerve pain that can last weeks or months.

- Immunocompromised patients: Risk of disseminated infection (e.g., pneumonia, hepatitis, meningoencephalitis).

Laboratory Diagnosis

Although clinical features are usually sufficient for diagnosis, several laboratory methods help confirm infection ⤵

1. PCR (Polymerase Chain Reaction)

- Most sensitive and specific test for detecting VZV DNA.
- Used on vesicle fluid, lesion scrapings, or CSF in encephalitis cases.
- Rapid and reliable ⚡

2. DFA (Direct Fluorescent Antibody) Test

- Detects viral antigens in lesion specimens.

- Can differentiate VZV from HSV lesions under fluorescence microscopy.

🔍 3. Tzanck Smear (Presumptive Test)

- Shows multinucleated giant cells 👀
- Cannot distinguish between VZV and HSV — both produce similar cytopathic effects.

🧫 4. Viral Culture

- Definitive method, though slow.
- Virus is isolated in cell culture and identified using specific antiserum.

💉 5. Serology

- Rising antibody titers indicate recent infection (useful for varicella).
- Less useful for zoster due to preexisting antibodies from prior varicella infection.

💊 Treatment

🧒 In Immunocompetent Children

- Usually no antiviral therapy required for *chickenpox* or *zoster* (mild course).

🧍 In Immunocompetent Adults

- Acyclovir (oral/IV) is often given:
  - Reduces duration & severity of symptoms.
  - Decreases viral shedding.

🏥 In Immunocompromised Patients

- Acyclovir (IV) is essential for:
  - Chickenpox
  - Zoster
  - Disseminated infection

- If acyclovir-resistant, use Foscarnet.

💊 Alternative Antivirals

Drug	Trade Name	Use	Effect

Famciclovir	Famvir	Zoster	Speeds healing, may reduce PHN
Valacyclovir	Valtrex	Zoster	Similar to famciclovir
Foscarnet	–	Acyclovir-resistant cases	Inhibits viral DNA polymerase

🧠 *Note:* None of these antivirals eliminate the latent virus in ganglia.

⚡ Treatment of Postherpetic Neuralgia (PHN)

- Pain management:
  - *Gabapentin*
  - *Lidocaine patches*
  - Occasionally, *tricyclic antidepressants*

🛡️ Prevention

💉 1. Vaccines

Vaccine	Type	Target	Key Notes

Varivax	Live attenuated	Prevents *Varicella (chickenpox)*	For children (1–12 yrs)
Zostavax	Live attenuated (14× higher viral dose than Varivax)	Prevents *Zoster (shingles)*	For adults >50 yrs
Shingrix	Recombinant glycoprotein vaccine	Prevents *Zoster*	Higher efficacy, especially in elderly

🔷 Zoster vaccines reduce zoster symptoms and PHN, but do not eradicate latency.

🔷 Live vaccines (Varivax, Zostavax) are contraindicated in:

- Immunocompromised individuals
- Pregnant women 🤰

💉 2. Passive Immunization

- Varicella-Zoster Immune Globulin (VZIG):
    - Contains high-titer antibodies to VZV.
    - Used for post-exposure prophylaxis in:
        - Immunocompromised persons
        - Newborns of infected mothers

- Susceptible pregnant women

💊 3. Chemoprophylaxis

- Acyclovir can be used prophylactically in immunocompromised contacts to prevent varicella or disseminated zoster.

🌾 Summary Flowchart

Exposure to VZV

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Clinical diagnosis (rash pattern, age, history)

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Confirm with PCR / DFA / Tzanck test

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┌> Immunocompetent child → Supportive care only
│
├> Adult (moderate/severe) → Acyclovir therapy
│
└> Immunocompromised patient → Acyclovir IV (→ Foscarnet if resistant)

↓

Prevent future infections →

Vaccination (Varivax / Zostavax / Shingrix)

Or

Passive prophylaxis with VZIG for high-risk exposed individuals 🤚

🧬 Cytomegalovirus (CMV)

🦠 Diseases Caused

- Congenital Cytomegalic Inclusion Disease 👶
    - *Most common cause of congenital abnormalities in the U.S.*
- Pneumonia & other infections in immunocompromised patients, such as:

- Bone marrow / stem cell transplant recipients
- Solid organ transplant patients

- Heterophil-negative Mononucleosis 💧

  - Seen in immunocompetent adults, clinically resembling EBV mononucleosis.

🧫 Important Properties

- Belongs to Herpesviridae family.

- Structurally & morphologically similar to HSV, but antigenically distinct.

- Single serotype.

- Humans are the only natural hosts 🌍

  - Animal CMV strains do not infect humans.

- Cytomegalo = "giant cell" → forms large cells with intranuclear inclusions.

🔄 Summary of Replicative Cycle

- Similar to Herpes Simplex Virus (HSV) cycle.
- Unique feature:
    - CMV virion brings some mRNAs for immediate early proteins directly into the host cell.
    - These mRNAs are translated immediately after entry, *before* new transcription begins.

🤧 Transmission & Epidemiology

Modes of transmission:

- Congenital (Transplacental) → Fetal infection 👶
- Perinatal: During passage through birth canal
- Postnatal: Via breast milk 🍼
- Saliva: Common in young children
- Sexual contact: Virus in semen & cervical secretions

- Blood transfusions & organ transplants 💉

Epidemiology:

- Worldwide distribution 🌎
- >80% of adults have CMV antibodies
- High seroprevalence increases with age and socioeconomic factors

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🧠 Pathogenesis & Immunity

Maternal primary infection →

↓

Transplacental spread to fetus →

↓

Fetal infection →

↓

Cytomegalic inclusion disease →
Multinucleated giant cells with intranuclear inclusions →

↓

Widespread organ damage →
Congenital abnormalities (especially if infection occurs in 1st trimester)

Congenital CMV Infection

- Occurs primarily when mother acquires CMV for the first time during pregnancy (no preexisting antibodies).
- Maternal antibodies can prevent fetal infection if mother had prior exposure.
- First trimester infection → highest risk of severe congenital defects, because organogenesis occurs then.

Common congenital abnormalities:

Affected System	Examples
CNS	Microcephaly, intracranial calcifications, hearing loss, developmental delay

Liver/Spleen	Hepatosplenomegaly, jaundice
Eyes	Chorioretinitis
General	Growth retardation, purpura ("blueberry muffin" rash)

🧒 Postnatal / Adult CMV Infections

- Usually asymptomatic in healthy individuals.
- May cause heterophil-negative mononucleosis with:
    - Fever, lymphocytosis, mild hepatitis
    - Negative Monospot test (unlike EBV)

⚠ Immunocompromised Patients

- Major cause of morbidity and mortality in transplant recipients.
- Diseases include:
    - Interstitial pneumonia
    - Retinitis (especially in AIDS)
    - Esophagitis, colitis, encephalitis

Latency & Reactivation

- CMV establishes latency in monocytes, macrophages, and bone marrow progenitor cells.
- Reactivation occurs when cell-mediated immunity decreases (e.g., after transplantation or during AIDS).
- Virus may also persist in kidneys for years.
- Reactivation in cervical cells → infection of newborn during birth.

Immune Evasion Mechanisms

- Latent State Maintenance:
  CMV remains latent for long periods due to immune evasion strategies.

1 Impaired Antigen Presentation:

  - MHC class I-viral peptide complex is unstable in CMV-infected cells.
  - → Viral antigens not displayed on cell surface →

Cytotoxic T cells fail to recognize infected cells.

2 microRNA-Mediated Suppression:

- CMV encodes microRNAs that bind to mRNA for class I MHC → prevents its translation.
- → No MHC class I expression → No killing by cytotoxic T cells.

3 Chemokine Receptor Mimicry:

- CMV encodes a viral chemokine receptor protein.
- Released protein binds to host chemokines, blocking leukocyte migration to infection site.

4 Immunosuppressive Effect:

- CMV inhibits T-cell function, contributing to immunosuppression.
- Both humoral and cell-mediated immunity play roles, but cell-mediated is more important.

Clinical Findings

🍼 Congenital (Cytomegalic Inclusion Disease)

- Occurs in ~20% of congenitally infected infants.
- Symptoms:
  - Microcephaly 🧠
  - Seizures ⚡
  - Deafness 👂
  - Jaundice & Hepatosplenomegaly 🤍
  - Purpura ("Blueberry muffin" lesions) — due to thrombocytopenia.
- Complication: Major cause of mental retardation in the U.S.
- Note: Infected infants may shed CMV in urine for years.

🧒 In Immunocompetent Adults

- Heterophil-negative mononucleosis-like illness:
  - Fever 🌡️
  - Lethargy 😴

- Abnormal lymphocytes on peripheral smear.
- Negative Monospot test (unlike EBV).

🫓 In Immunocompromised Hosts

- Transplant recipients:
  - Pneumonitis, Hepatitis, Esophagitis.
- AIDS patients:
  - Retinitis 👁 → blindness
  - Colitis → chronic diarrhea
  - Anemia & thrombocytopenia common.

🔬 Laboratory Diagnosis

Method	Principle	Notes
PCR for CMV DNA/RNA	Detects viral genome	Used in CSF, amniotic, or blood samples
Shell vial culture + Immuno fluorescent Ab	Detects early CMV antigen	Rapid (within 72 hours)

Histology	Intranuclear "Owl's eye" inclusion bodies 	Seen in urine or tissue samples
Serology (IgM)	Detects recent infection	Useful in congenital or primary infection
pp65 antigenemia	Immunofluorescent detection in leukocytes	Indicates active replication

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Treatment

Drug	Route	Notes
Ganciclovir (Cytovene)	IV	Effective for retinitis & pneumonia
Valganciclovir	Oral	Prodrug of ganciclovir; used for CMV retinitis
Foscarnet (Foscavir)	IV	Used in resistant strains; more side effects
Cidofovir (Vistide)	IV	Alternative therapy
Fomivirsen (Vitravene)	Intraocular	Antisense DNA; used for CMV retinitis
Acyclovir	—	✕ Largely ineffective against CMV

Resistance: Due to mutations in UL97 gene (viral phosphokinase).

 Prevention

- No vaccine available ⃠
- Ganciclovir prophylaxis in high-risk AIDS or transplant patients.
- CMV-negative blood for transfusion to neonates.
- CMV-negative organ donors for seronegative recipients.
- High-titer CMV immune globulin (CytoGam) for organ transplant recipients.
- Isolation of infected infants (shedding virus in urine).

Epstein-Barr Virus (EBV)

(Human herpesvirus-4 — DNA virus, enveloped, icosahedral capsid)

Diseases Caused

- Infectious mononucleosis ("kissing disease")
- Burkitt's lymphoma (endemic African type)
- Other B-cell lymphomas (esp. immunocompromised)
- Nasopharyngeal carcinoma
- Oral hairy leukoplakia (in AIDS patients)

Important Properties

- Family: Herpesviridae
- Structure: Similar to HSV; antigenically distinct.

- Key Antigens:

Antigen	Description	Diagnostic Use
Viral capsid antigen (VCA)	Major structural antigen	🧪 Main diagnostic marker
Early antigen (EA)	Made before DNA synthesis	Indicates active infection
Epstein–Barr nuclear antigen (EBNA)	Bound to host chromosomes	Marker of latent infection
Viral membrane antigen (VMA)	On virion envelope	Induces neutralizing Ab

- Host: Humans only 🧍
- Target cells:
    - B lymphocytes (via C3d receptor / CD21)
    - Pharyngeal epithelial cells → sore throat
- Latency:
    - EBV DNA remains episomal (not integrated) in B cells.
    - Only subset of viral genes expressed during latency.

🔁 Replication Summary

- Similar to HSV cycle.
- Entry via CD21 (C3d complement receptor) on B cells.
- Productive infection → viral replication → latency in memory B cells.

🌍 Transmission & Epidemiology

- Route: Saliva exchange ("kissing")
- Reservoir: Humans with active or latent infection (virus in saliva).
- Rarely: Blood transmission.
- Prevalence: >90% adults seropositive worldwide 🌐
- Age pattern:
    - Early childhood: Asymptomatic (esp. low-SES populations).
    - Adolescents/young adults: Symptomatic infectious mononucleosis (esp. college students).

⚔ Pathogenesis

1. Initial infection:
    - Begins in oropharyngeal epithelium → spreads to bloodstream.
2. Target cells:
    - B lymphocytes infected → proliferation.
3. Immune response:
    - Cytotoxic T cells attack infected B cells → form atypical lymphocytes (Downey cells) 🥯
4. Latency:
    - EBV persists in memory B cells lifelong.

Immunity & Serologic Response

Antibody	Timing	Significance
IgM to VCA	Appears early	Indicates acute infection
IgG to VCA	Persists for life	Indicates past infection / immunity
Heterophil antibodies	Appear during illness	Basis of Monospot test
Antibody to EBNA	Appears later	Marker of convalescence / past infection

- Heterophil antibodies:
  - Non-EBV-specific ("heterophil" = reacts with unrelated antigens).
  - Agglutinate sheep/horse RBCs
  - Removed by adsorption with guinea-pig kidney extract to exclude Forssman antibodies.
  - Disappear within 6 months after recovery.

- Can also appear in hepatitis B and serum sickness (so not specific).

💡 Key Diagnostic Clues

- Monospot test positive (heterophil antibody).
- Atypical lymphocytes (T cells) on blood smear.
- Serology: IgM anti-VCA = acute; IgG anti-VCA ± anti-EBNA = past infection.

🧍 Summary Table

Feature	EBV	CMV
Typical host	Adolescents/young adults	Neonates, immunocompromised
Monospot test	☑ Positive	✗ Negative
Latency	B lymphocytes	Monocytes, macrophages
Main complication	Lymphomas, carcinoma	Retinitis, colitis
Transmission	Saliva	Saliva, sexual,

🩺 Clinical Findings

1. Infectious Mononucleosis (IM)

- Classic triad:
  - Fever 🌡️
  - Sore throat 😂
  - Lymphadenopathy (especially posterior cervical nodes)
- Other findings:
  - Splenomegaly (⚠️ risk of rupture with contact sports)
  - Hepatitis (mild to moderate elevation of transaminases)
  - Encephalitis (rare)
  - Fatigue, anorexia, malaise
- Course: Usually resolves in 2–3 weeks spontaneously.

2. Severe Progressive Mononucleosis (X-linked lymphoproliferative syndrome)

- Occurs in boys with X-linked immune deficiency (defective NK and T-cell function).
- Very severe, often fatal (75% mortality by age 10) ⚠
- Treatment: Bone marrow / cord blood transplant may cure.

3. Hairy Leukoplakia

- White, "hairy" lesion on lateral tongue surface.
- Non-malignant, caused by EBV replication in epithelial cells.
- Seen in AIDS and immunocompromised patients.

4. EBV-Associated Malignancies

Malignancy	Site / Population	Mechanism
Burkitt's lymphoma	Endemic in African children	EBV + c-myc translocation

Hodgkin's lymphoma (some types)	Worldwide	EBV-infected Reed-Sternberg cells
Nasopharyngeal carcinoma	Common in Chinese population	Latent EBV in epithelial cells
Thymic carcinoma	Rare (USA)	EBV genome in tumor cells
Post-transplant lymphoproliferative disorder (PTLD)	After bone marrow / organ transplant	Immunosuppression allows uncontrolled B-cell growth

- Key point: EBV initiates proliferation, but additional mutations cause malignancy.
- Reduced cell-mediated immunity → uncontrolled EBV-infected B-cell growth.

Laboratory Diagnosis

1. Serologic Tests (Mainstay)

(a) Heterophil Antibody Test

- Detects heterophil antibodies (non-EBV-specific).

- Positive by week 2 of illness.
- Monospot test: modern version → more sensitive, specific, and cheaper.
- Useful for acute diagnosis, not past infection (antibody declines after recovery).

(b) EBV-Specific Antibody Tests

Antibody	Timing	Diagnostic use
IgM anti-VCA	Early	Acute infection
IgG anti-VCA	Persists for life	Past infection
Anti-EA / Anti-EBNA	Later	Confirms infection stage (EBNA = latent marker)

2. Blood Findings

- Absolute lymphocytosis (↑ lymphocytes).
- Up to 30% atypical lymphocytes (cytotoxic T cells reacting to infected B cells).
    - Large cells, abundant vacuolated cytoplasm,

indented nucleus (Downey cells ).

3. Molecular Methods

- PCR for EBV DNA: used in
    - Difficult-to-diagnose infections
    - Post-transplant lymphoproliferative disorder (PTLD)

4. Virus Isolation (rarely used)

- Detected by transformation of cord blood lymphocytes, followed by fluorescent antibody staining for EBNA (technically difficult).

Treatment

Condition	Recommended Approach
Uncomplicated IM	Supportive care only (rest, hydration, avoid sports)
Severe / life-	High-dose acyclovir may help

threatening
EBV infections

PTLD or lymphoma	Reduce immunosuppression + chemotherapy

(Acyclovir has little activity vs. EBV but may reduce viral shedding.)

Prevention

- No vaccine available.
- Avoid sharing drinks or kissing during active infection.
- Transplant patients: reduce immunosuppression if EBV reactivation suspected.

EBV & Oncogenesis

Key Concept: EBV immortalizes B lymphocytes → uncontrolled proliferation.

Mechanism in Burkitt's Lymphoma:

- Translocation of c-myc oncogene (chromosome 8) → near immunoglobulin gene promoter (chromosome 14).

- Overexpression of c-Myc protein → ↑ transcription of cell-cycle-activating kinases → uncontrolled growth

☑ Summary Flowchart

Primary EBV infection →

↓

Infection of oropharyngeal epithelium →

↓

Spread to B lymphocytes →

↓

T-cell response → atypical lymphocytes (Downey cells) → clinical mononucleosis

↓

Latency in B cells → reactivation possible under immunosuppression

↓

Chronic infection or immunosuppression →

↳ Hairy leukoplakia (AIDS)
↳ Post-transplant lymphoproliferative disorder (PTLD)
↳ Burkitt's lymphoma, Hodgkin's lymphoma, Nasopharyngeal carcinoma

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Human Herpesvirus-8 (HHV-8) / Kaposi's Sarcoma - Associated Herpesvirus

Introduction

- Discovered in 1994.
- Also called Kaposi's sarcoma-associated herpesvirus (KSHV).
- Causes Kaposi's Sarcoma (KS) — most common cancer in AIDS patients.
- Belongs to Gammaherpesvirus subfamily (like EBV).

🔬 Epidemiologic Clues

- KS common in sexually acquired HIV, but rare in transfusion-acquired HIV → hinted at a second sexually transmitted virus.

- HHV-8 DNA found in >90% of KS lesions, absent in tissues of AIDS patients without KS.

- Antibodies to HHV-8 found in:

    - Most HIV-positive patients with KS ✅
    - Few HIV-positive patients without KS ❌
    - Rare in HIV-negative STD patients ❌

- Seroprevalence:

    - ~3% in U.S. and England
    - ~50% in East Africa 🌍

🧠 Mechanism of Malignant Transformation

HHV-8 infection

↓

Expression of Latency-Associated Nuclear Antigen (LANA)

↓

LANA inactivates tumor suppressor genes (RB & p53)

↓

Uncontrolled proliferation of vascular endothelial cells

↓

Formation of spindle-shaped cells → Kaposi's Sarcoma

 Transmission

- Sexual contact (most common)
- Saliva
- Organ transplantation (esp. kidney → transplantation-associated KS)

Diseases Caused by HHV-8

Disease	Description	Pathogenesis
Kaposi's Sarcoma (KS)	Malignancy of vascular endothelial cells	Caused by inactivation of tumor suppressors by LANA
Primary Effusion Lymphoma (PEL)	Rare B-cell lymphoma, typically in AIDS patients	HHV-8 infects B cells → uncontrolled proliferation

Clinical Features of Kaposi's Sarcoma

- Lesion appearance:
  - Reddish-purple, flat or nodular lesions
  - Sites: Skin, oral cavity, soles (not palms)
- Histology:
  - Spindle-shaped endothelial cells, erythrocytes, and extravasated RBCs (→ purplish color)
- Internal involvement:

- Gastrointestinal tract and lungs commonly affected

🔬 Laboratory Diagnosis

Suspected KS lesion

↓

→ Biopsy of skin lesion

↓

→ Identify spindle cells histologically

↓

→ Detect HHV-8 DNA/RNA via PCR

↓

→ Confirms diagnosis ✅

🧪 Note: HHV-8 cannot be cultured in lab.

Treatment

Type	Description
Local Lesions	Surgical excision / Radiation / Chemotherapy
Immunomodulatory Therapy	Alpha-interferon
AIDS-related KS	HAART (Highly Active Antiretroviral Therapy) — effective for early KS
Antiviral drugs	Acyclovir, Foscarnet, Cidofovir are NOT effective ⃠

Prevention

- HAART reduces incidence of KS in HIV patients.
- No vaccine available yet.

Summary Table

Feature	HHV-8 / KSHV
Type of Virus	DNA virus, Herpesviridae family
Natural Host	Humans only
Transmission	Sexual, Saliva, Organ transplant
Main Disease	Kaposi's Sarcoma (AIDS patients)
Mechanism	LANA inactivates RB & p53
Other Diseases	Primary Effusion Lymphoma
Diagnosis	Biopsy + PCR
Treatment	HAART, Surgery, Interferon
Prevention	HAART (no vaccine)