

# **Latent Infections**

## **(Herpesvirus Infections)**

Persistence • Reactivation • Clinicopathologic consequences

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## Learning outcomes

- Define latency by viral-genome persistence and absence of infectious virion production.
- Classify the eight human herpesviruses by  $\alpha$ -,  $\beta$ -, and  $\gamma$ -group tropism.
- Explain how reactivation links a silent reservoir to tissue injury.
- Apply reservoir–disease correlations to HSV, VZV, CMV, and EBV.

## **What makes an infection latent?**

**Viral genome persists; Infectious virus is not produced.**

- The latent cell retains viral genetic material.
- Reactivation can restore replication and infectious virion release.

# Latency is not continuous productive infection

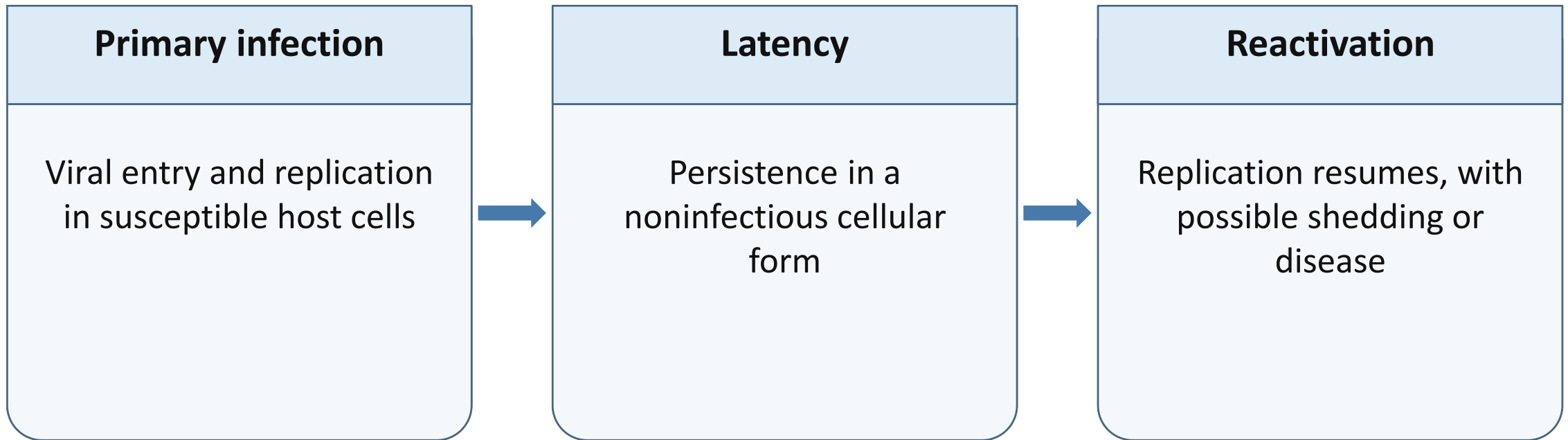
## Latent state

- Viral genomes persist inside host cells.
- No production of infectious virions.
- Symptoms may be absent despite persistence.

## Productive infection

- Viral replication generates infectious virus.
- Virions can spread to new cells or hosts.
- Tissue injury may accompany replication.

# The three-state herpesvirus course



**A clinically silent interval does not imply eradication.**

## **Reactivation is the proximate source of recurrent injury**

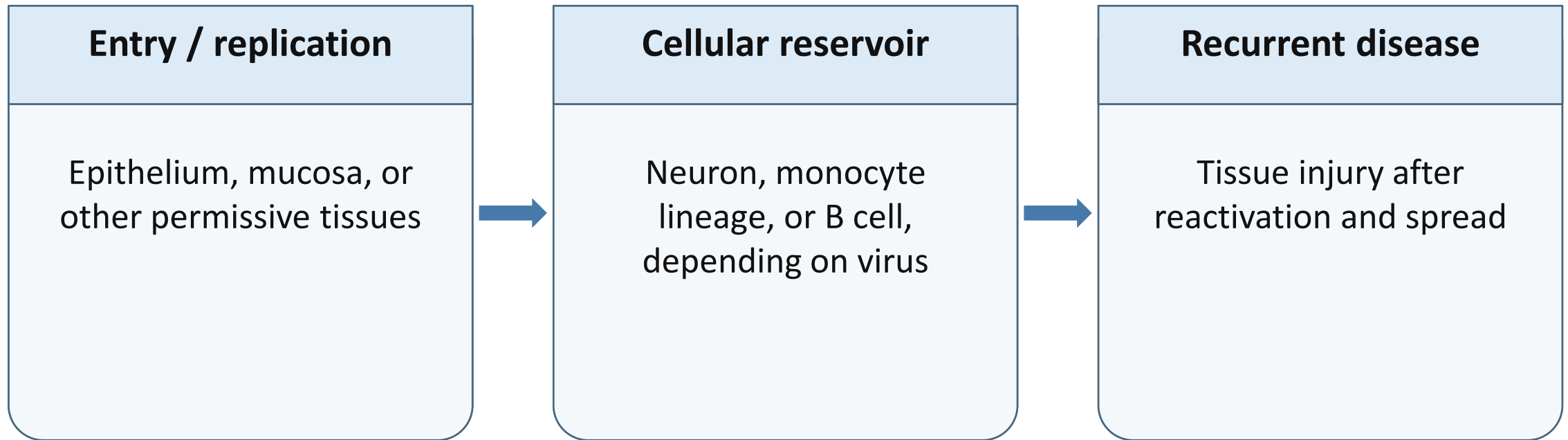
- Dormancy itself does not release infectious virions.
- Reactivation generates progeny virus capable of tissue spread.
- The resulting infection can injure target tissue directly or trigger immune-mediated damage.

## **Why “recovered” may not mean “cleared”**

**Resolution of the first episode  $\neq$  elimination of the reservoir.**

- Initial illness can subside while the viral genome persists.
- The same host may subsequently shed virus or develop recurrent disease.

# Different compartments perform different roles



**Reservoir location and lesion location are not always the same.**

## **Shedding and visible disease are not equivalent**

- Reactivation may occur with or without symptoms in HSV infection.
- Shedding demonstrates release of infectious virus, not necessarily overt tissue damage.
- Clinical silence should not be used to infer absence of reactivation.

## **Herpesvirus latency: A family-level strategy**

- Human herpesviruses frequently establish acute infection followed by lifelong persistence.
- The group contains large double-stranded DNA viruses.
- The Robbins overview describes approximately 70 encoded proteins.
- All three subgroups can reactivate; Their reservoirs are different.

# The eight human herpesviruses

## $\alpha$ -Herpesviruses

HSV-1, HSV-2, VZV

## $\beta$ -Herpesviruses

CMV, HHV-6, HHV-7

## $\gamma$ -Herpesviruses

EBV, KSHV / HHV-8

Subgroups are parallel classes defined by cell tropism and latency site.

# Classification by predominant latency compartment

| Subgroup | Members           | Dominant latency pattern |
|----------|-------------------|--------------------------|
| $\alpha$ | HSV-1; HSV-2; VZV | Postmitotic neurons      |
| $\beta$  | CMV; HHV-6; HHV-7 | Diverse cell types       |
| $\gamma$ | EBV; KSHV (HHV-8) | Mainly lymphoid cells    |

## Subgroup terminology predicts cellular tropism

- **$\alpha$  group** epithelial infection, then neuronal latency.
- **$\beta$  group** infection and latency across diverse cell types.
- **$\gamma$  group** predominant lymphoid-cell latency.
- The preferred reservoir helps predict the form of recurrence.

## Site of initial disease versus site of persistence

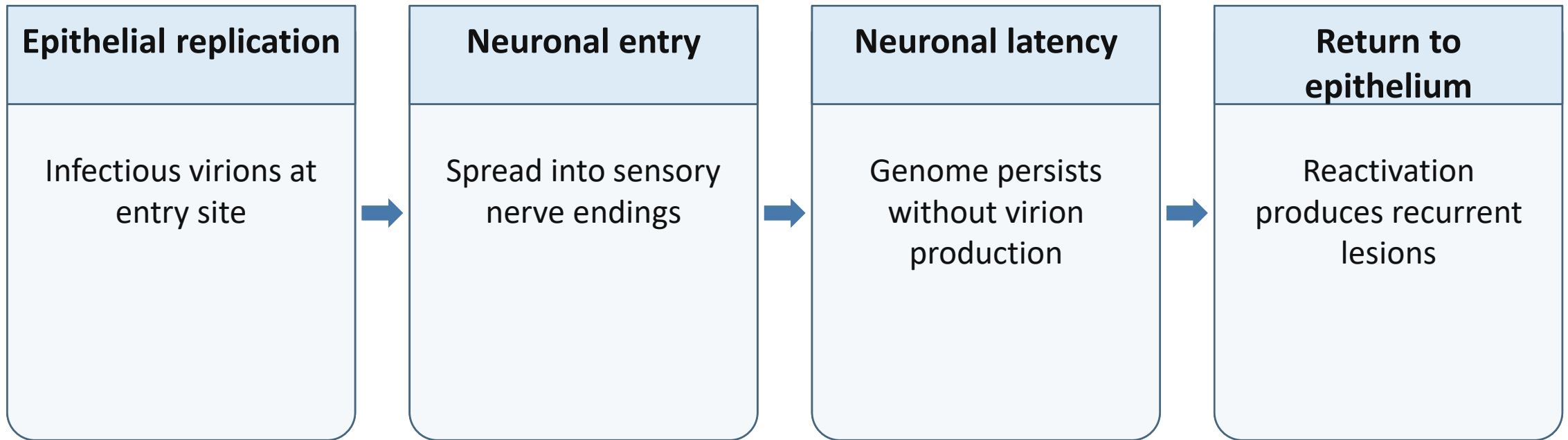
### Infection can be visible

- Mucocutaneous blisters during productive  $\alpha$ -herpesvirus infection.
- Multiorgan CMV infection with nuclear inclusion-bearing cells.
- Lymphoid expansion during symptomatic EBV infection.

### Persistence may be hidden

- Sensory neurons for HSV/VZV.
- Monocyte and precursor compartments for CMV.
- A restricted population of EBV-infected B cells.

# $\alpha$ -Herpesvirus: The conceptual blueprint

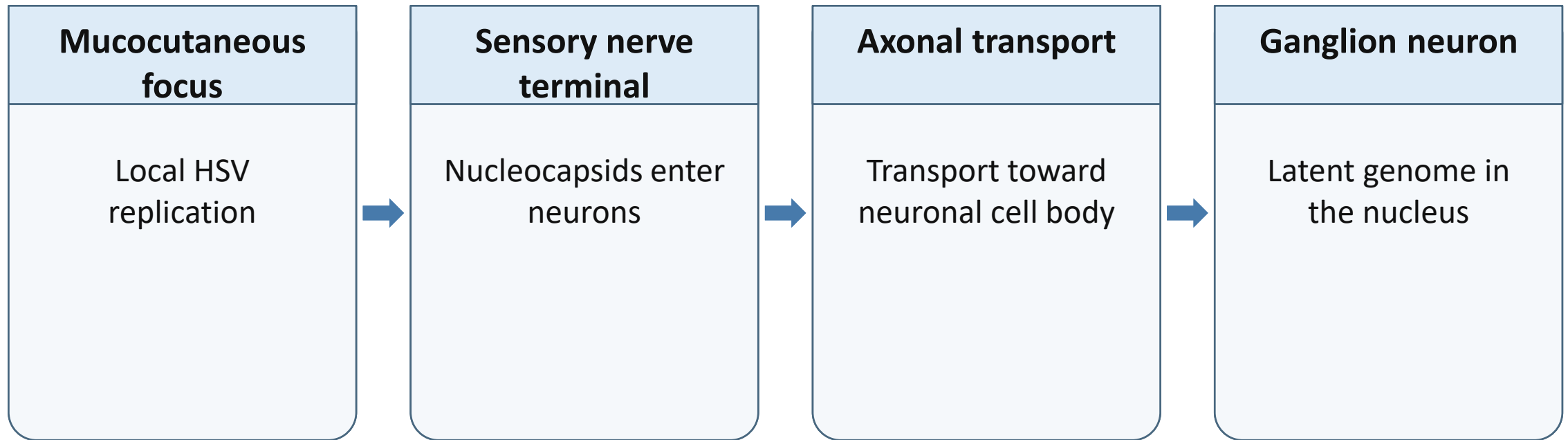


**HSV is the best-described model of this sequence.**

## **HSV begins with mucocutaneous replication**

- HSV-1 and HSV-2 usually replicate at oropharyngeal or genital entry sites.
- Epidermal and mucosal infection can generate intraepithelial vesicles.
- New virions are available to spread to adjacent neural structures.

# HSV uses sensory neurons to establish latency



**Anatomic transport explains persistence away from a healed lesion.**

## **The HSV latent genome remains nuclear**

**Viral DNA persists in the sensory-neuron nucleus.**

- Latency is nonproductive despite persistence of the viral genome.
- The neuron is a long-lived cellular reservoir.

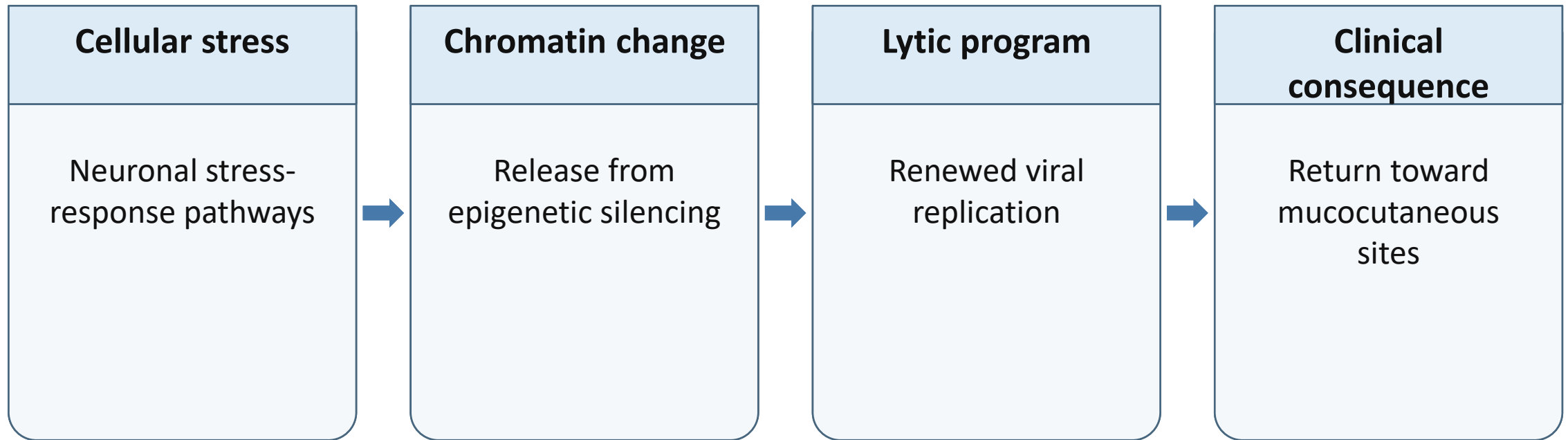
## **Latency-associated transcripts are a distinctive HSV feature**

- During HSV latency, latency-associated transcripts (LATs) are expressed.
- The source reports no detectable viral-protein production during this state.
- LAT expression distinguishes latent transcription from full lytic viral replication.

## **How LATs may promote HSV persistence**

- Proposed antiapoptotic activity may preserve infected neurons.
- Proposed chromatin-based silencing suppresses lytic gene expression.
- LAT-derived microRNAs may downregulate essential HSV lytic genes.

# HSV reactivation: A proposed molecular sequence



**Proposed mechanism; Not a universally specified trigger.**

## **Reactivation can recur despite existing immunity**

- HSV-1 and HSV-2 may reactivate repeatedly.
- Recurrences may be symptomatic or asymptomatic.
- Host immunity controls infection but may not remove the latent neuronal reservoir.
- Viral mechanisms impede both cellular and humoral immune recognition.

# Primary HSV infection and recurrent HSV infection

## Primary episode

- Entry-site epithelial replication.
- Local lesion with access to sensory nerves.
- Establishment of neuronal persistence.

## Recurrent episode

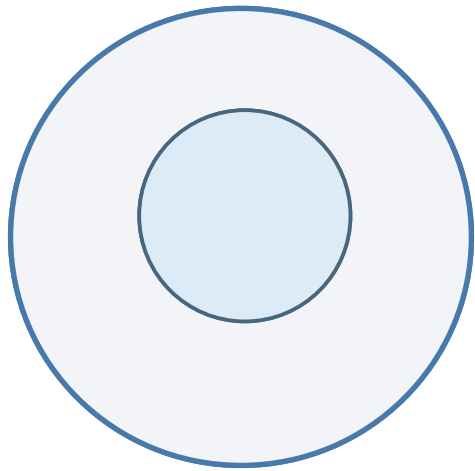
- Virus emerges from an already infected neuronal reservoir.
- Transport to epithelial target tissue.
- Often localized; May be clinically silent.

## **HSV lesions are consequences of active replication**

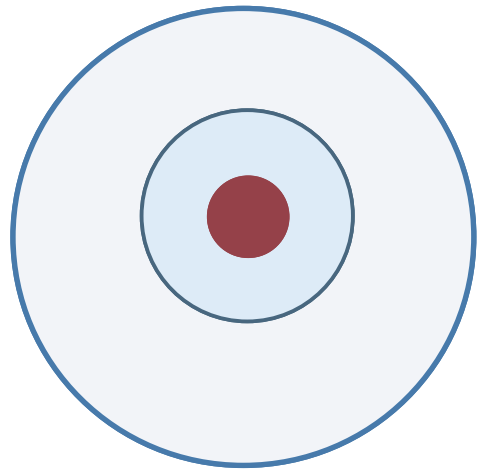
- Ballooning degeneration and intracellular edema produce intraepithelial vesicles.
- Vesicle rupture can leave crusted lesions or superficial ulcers.
- The infectious lesion is distinct from the silent ganglionic reservoir.

# HSV cytopathic changes: What a schematic can show

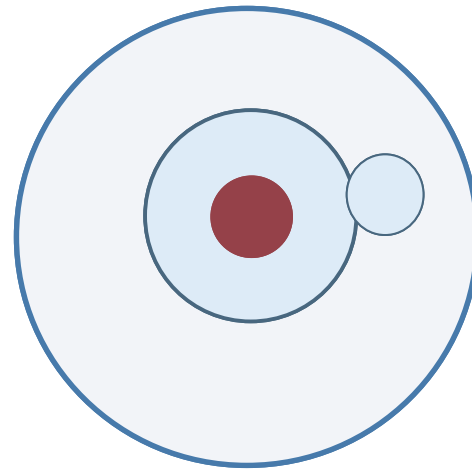
*Simplified cell schematic — not diagnostic histology*



**Epithelial cell**



**Nuclear inclusion**



**Fusion / cytopathic  
effect**

- Intranuclear Cowdry type A inclusions accompany productive HSV infection.
- Cell fusion can produce multinucleated epithelial syncytia.

## Why HSV inclusions are intranuclear

- Viral replication components and assembling virions accumulate in the nucleus.
- The host chromatin is displaced toward the nuclear margin.
- The resulting Cowdry type A inclusion is a sign of active infection, not latent carriage.

# HSV vesicular lesions need clinical context

## Oral / facial disease

- Cold sores favor skin bordering mucosal openings.
- Often bilateral and not dermatomally restricted.
- Gingivostomatitis may be prominent in children.

## Genital disease

- Genital mucosal vesicles evolve into superficial ulcers.
- HSV-2 is more frequent than HSV-1 as a cause.
- Primary and recurrent patterns are possible.

# HSV keratitis: Two mechanisms of damage

## Epithelial keratitis

- Direct viral cytolysis injures superficial epithelium.
- Active replication is central to tissue injury.

## Stromal keratitis

- Mononuclear infiltration and neovascularization.
- Immune-mediated tissue injury drives scarring and opacification.

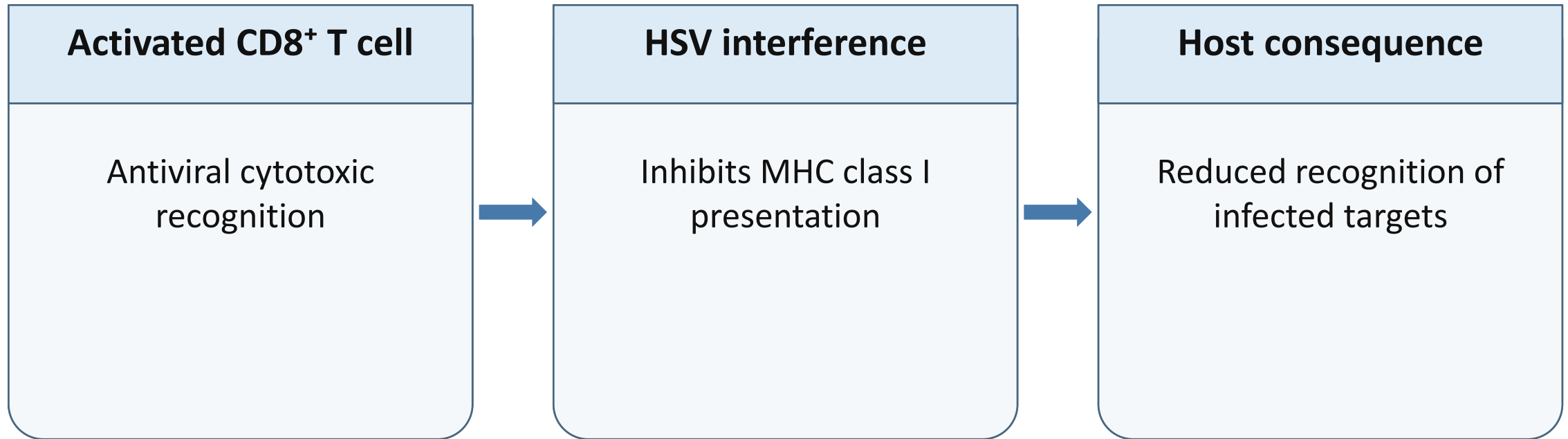
## **HSV encephalitis can cause severe CNS injury**

- HSV-1 is an important cause of sporadic fatal encephalitis.
- Brain involvement often favors temporal lobes and orbital frontal gyri.
- Defects in TLR3 or its signaling components increase susceptibility.

## **Impaired host defenses change HSV severity**

- Neonates may develop disseminated infection with multiorgan necrosis.
- Patients receiving chemotherapy or with impaired cellular immunity may develop widespread disease.
- HSV may produce esophagitis, necrotizing bronchopneumonia, or hepatitis.

# HSV evasion of cellular immunity



# HSV evasion of antibody and complement

## Viral glycoprotein gE

- Binds Fc portion of IgG.
- Interferes with complement C1q engagement.
- Disrupts antibody-dependent effector responses.

## Viral glycoprotein gC

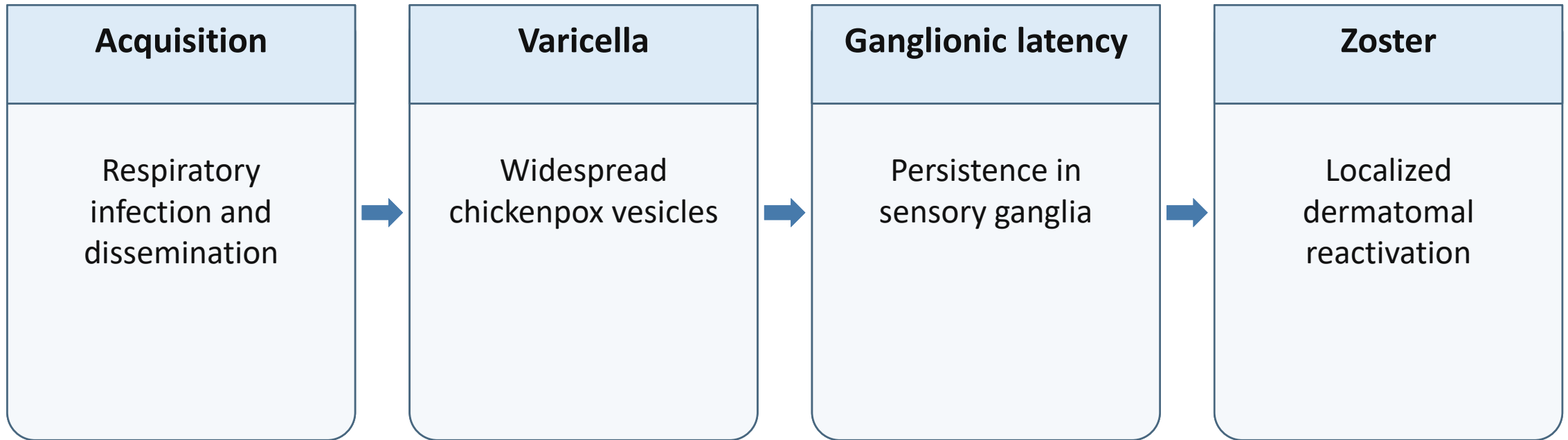
- Interacts with complement C3 / activation products.
- Accelerates decay of complement components.
- Weakens alternative-pathway defense.

## **Why HSV can recur in an immune host**

**Immune control is not sterilizing eradication.**

- Neuronal latency shields a persistent genetic reservoir.
- Reacting to reactivation may limit disease without preventing the next episode.

# VZV separates primary and recurrent syndromes



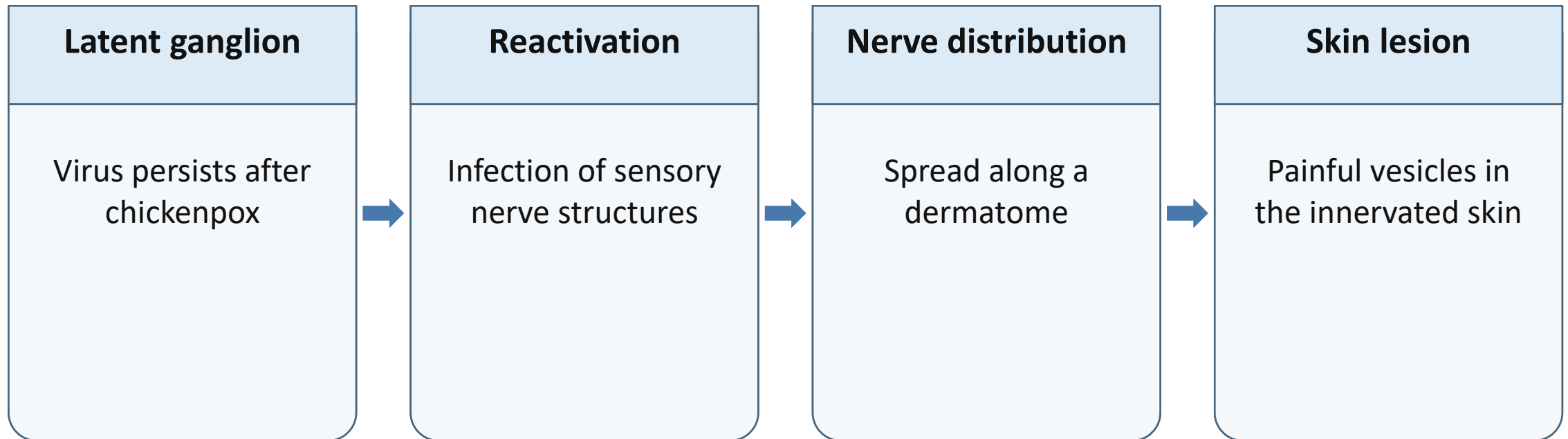
## **Primary VZV follows a systemic dissemination route**

- VZV is spread through respiratory aerosols.
- Hematogenous dissemination causes widespread vesicular lesions.
- This differs from the usually localized mucocutaneous entry-site disease of HSV.

## **VZV latency resides in sensory ganglia**

- VZV persists in ganglionic neurons and/or nearby satellite cells.
- Dorsal root and trigeminal sensory ganglia are important reservoirs.
- A long interval may separate chickenpox from shingles.

# Anatomic origin of a zoster eruption



## Why shingles hurts

- Ganglionic and neural inflammation accompanies reactivation.
- The source describes mononuclear infiltrates and neuronal injury in affected ganglia.
- Pain, burning, and itching can accompany the cutaneous vesicles.

## **Varicella and zoster share a cytopathic lesion**

- Both can generate intraepithelial vesicles with intranuclear inclusions.
- Primary varicella crops are generalized and may appear in successive waves.
- Zoster is usually localized to the distribution of affected sensory nerves.

# HSV versus VZV: Important differences

## HSV

- Usually replicates at oral or genital entry sites.
- Recurrent episodes may be frequent and nondermatomal.
- Latent HSV DNA is retained in sensory neurons.

## VZV

- Primary infection includes viremia and widespread varicella.
- Reactivation typically produces a dermatomal shingles eruption.
- Pain reflects concomitant neural inflammation.

## **$\beta$ -Herpesviruses differ in cellular reservoirs**

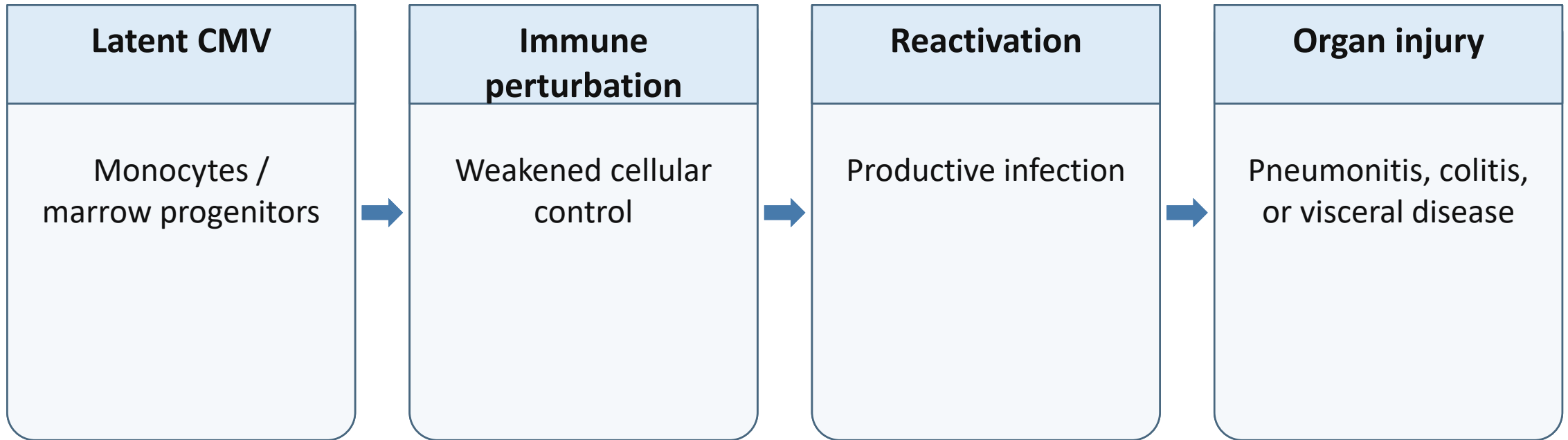
**A diverse cell repertoire replaces a single neuron-centered model.**

- CMV, HHV-6, and HHV-7 are the named  $\beta$ -group members.
- The subgroup infects and establishes latency in several cell types.

## **CMV has a hematopoietic reservoir**

- CMV latency occurs in monocytes and bone marrow progenitors.
- Depression of cellular immunity may allow CMV reactivation.
- Productive disease can involve epithelial, endothelial, and other parenchymal cells.

# CMV: Reservoir to opportunistic disease

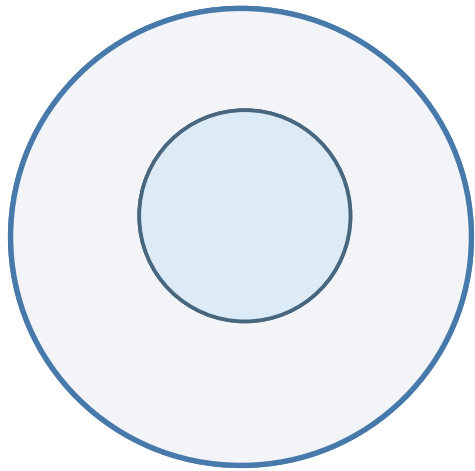


## **CMV virulence depends strongly on immune status**

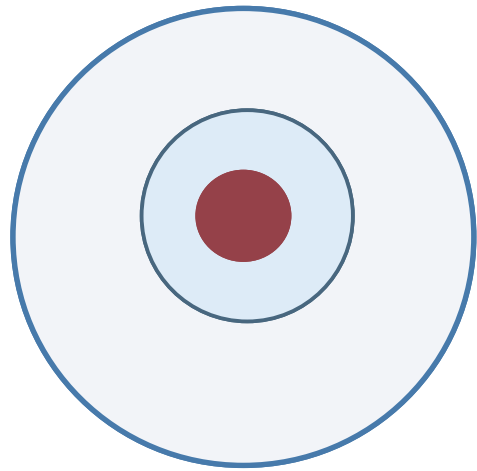
- Many immunocompetent hosts have asymptomatic or mononucleosis-like illness.
- Neonates may develop serious congenital or perinatal infection.
- Transplant recipients and severely immunosuppressed patients risk organ disease.

# CMV “owl’s-eye” change is a productive-infection clue

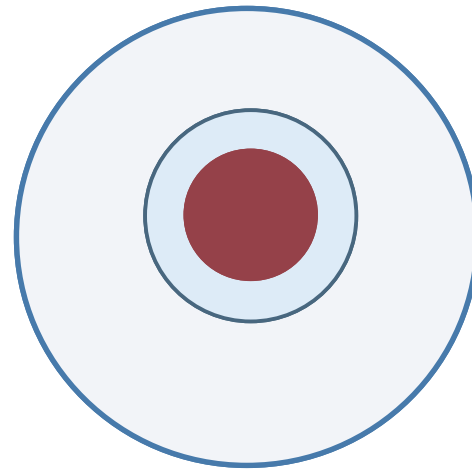
*Simplified cell schematic — not diagnostic histology*



**Uninfected cell**



**Enlarging infected cell**



**Prominent nuclear inclusion**

- Affected cells and nuclei enlarge; An inclusion has a clear peripheral halo.
- The drawing is schematic; Definitive morphologic recognition requires genuine tissue.

## **CMV may damage tissue with little inflammation**

- The source describes focal necrosis in many different organs.
- Some infected tissues show comparatively little inflammatory response.
- This explains why severe organ injury can coexist with limited cellular reaction.

# CMV control: Virus versus immune host

## Viral immune evasion

- Downmodulates MHC I and II molecules.
- Modulates cytokine signaling and NK-cell recognition.
- Can impair dendritic-cell function.

## Host control

- CD8<sup>+</sup> T cells are important effectors.
- CD4<sup>+</sup>,  $\gamma\delta$  T cells, and NK cells also contribute.
- Cellular immunodeficiency facilitates organ disease.

## Two clinically distinct CMV contexts

### **Congenital CMV**

- Fetal acquisition via transplacental spread.
- Possible microcephaly, calcifications, or sensorineural deficits.
- Not necessarily a reactivation syndrome.

### **Post-transplant CMV**

- May represent new infection or latent-virus reactivation.
- Can cause pneumonitis and severe colitis.
- Quantitative PCR is used in monitoring.

## **CMV diagnosis depends on the clinical question**

- Tissue histology can show characteristic cytomegalic inclusions.
- PCR detects CMV DNA; Quantitative PCR supports transplant monitoring.
- Congenital CMV can be diagnosed by PCR testing of urine or saliva.
- Detection and attributable organ disease are not identical questions.

## **HHV-6 and HHV-7 complete the $\beta$ group**

- Both are classified with CMV in the  $\beta$ -herpesvirus subgroup.
- They cause exanthem subitum (roseola infantum, sixth disease).
- These infections exemplify viral latency beyond HSV, VZV, and CMV.

## **HHV-6/7 reactivation may affect multiple organs**

- The textbook associates reactivation with encephalitis.
- Pneumonitis and hepatitis are also described associations.
- Myelitis is among the reported neurologic complications.
- An association in the overview should not be mistaken for a universal outcome.

## **$\gamma$ -Herpesviruses favor lymphoid latency**

**Persistent infection is mainly maintained in lymphoid cells.**

- The  $\gamma$  group includes EBV and Kaposi sarcoma herpesvirus (KSHV / HHV-8).
- EBV illustrates how latency intersects with lymphocyte activation.

# EBV-infected B cells: Two outcomes

## Lytic EBV infection

- Minority of infected B cells undergo productive replication.
- Cell lysis releases new virions.

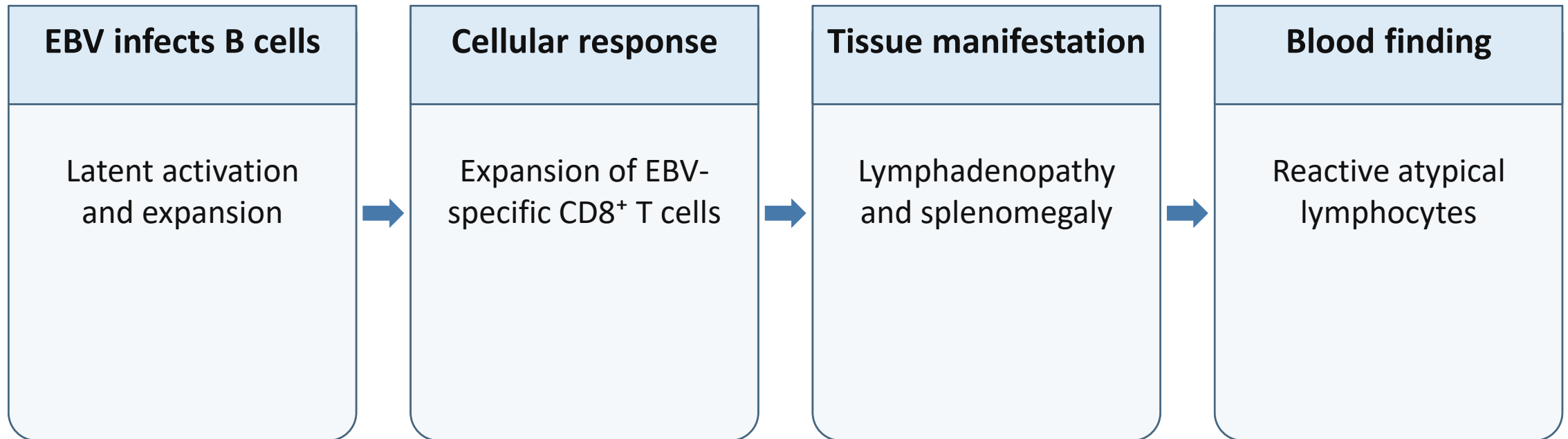
## Latent EBV infection

- Most infected B cells support persistent viral genomes.
- The genome persists as an extrachromosomal episome.

## **EBV latency can initially promote B-cell expansion**

- Latent viral products include LMP1 and EBNA2.
- These proteins support activation and proliferation of infected B cells.
- The ensuing polyclonal B-cell response produces diverse antibodies.

# Why EBV mononucleosis yields atypical T cells



## **The conspicuous EBV blood cell is often not infected**

- The large atypical lymphocytes in mononucleosis are mainly reactive CD8<sup>+</sup> T cells.
- These lymphocytes respond to EBV-infected B cells.
- The diagnostic appearance reflects the host response, not direct infection of every atypical cell.

## **Reactive EBV lymphadenopathy can mimic lymphoma**

- Expansion of T-cell-rich paracortical areas may be striking.
- A minority of EBV-infected B cells express latency-associated proteins.
- The exuberant reactive appearance may require discrimination from malignant lymphoma.

## **Immune surveillance changes EBV persistence**

- Effective host responses restrict viral shedding and highly immunogenic infected B cells.
- Some B cells reduce expression of viral proteins and survive indefinitely.
- Acquired cellular immune dysfunction can permit pathologic B-cell expansion.

## **EBV links latency to a neoplastic risk context**

- EBV is associated with certain lymphomas and nasopharyngeal carcinoma.
- Immunosuppression can release restraint on EBV-infected B-cell populations.
- Latent EBV infection alone is not equivalent to a cancer diagnosis.

## **KSHV / HHV-8 belongs in the $\gamma$ -group map**

- KSHV is the eighth named human herpesvirus in this taxonomy.
- Its classified latency is mainly lymphoid, as for other  $\gamma$ -group viruses.
- Detailed KSHV-associated neoplasia is beyond the cited latency overview.

## **Monkey B virus: A zoonotic boundary case**

**Herpesvirus simiae can cause severe neurologic disease after monkey bites.**

- It is an Old World monkey virus with similarities to HSV-1.
- Animal handlers may acquire a potentially fatal neurologic infection.
- It is separate from the eight listed human herpesviruses.

## Synthesis: Reservoir, reactivation, and pathology

| Virus         | Predominant reservoir | Illustrative consequence                       |
|---------------|-----------------------|------------------------------------------------|
| HSV-1 / HSV-2 | Sensory neuron        | Recurrent mucocutaneous infection              |
| VZV           | Sensory ganglion      | Dermatomal shingles                            |
| CMV           | Monocyte / progenitor | Pneumonitis or colitis under immunosuppression |
| EBV           | B lymphocyte          | Mononucleosis; pathologic B-cell expansion     |

## Evidence of prior infection versus active disease

### Historical / reservoir evidence

- Past infection may leave viral genomes in host cells.
- Some antiviral antibodies persist after recovery.
- Persistence need not be symptomatic.

### Evidence of productive pathology

- Compatible tissue injury or cytopathic change.
- Appropriately interpreted virologic detection.
- Clinical distribution and immune status.

## Select testing to match the herpesvirus syndrome

- **VZV** PCR is the principal diagnostic method in the adjacent description.
- CMV tissue morphology and PCR; Quantitative PCR for transplant monitoring.
- **EBV mononucleosis** atypical lymphocytes, heterophile testing, and EBV-specific serology.
- Morphology and laboratory detection require appropriate clinicopathologic interpretation.

# Application: Recurrent oral vesicles

## CLINICAL VIGNETTE

An otherwise healthy person has episodic vesicles near the lip after a prior similar episode.

**Where is the most relevant silent reservoir?**

**Interpretation: Sensory neurons**

Reasoning: HSV can remain latent in the sensory ganglia after mucosal or skin lesions heal.

## **Application: Painful unilateral rash**

### **CLINICAL VIGNETTE**

An older adult develops a painful vesicular eruption confined to a band of skin on one side.

**Which mechanism best explains the distribution?**

**Interpretation: Reactivated VZV in a sensory ganglion**

Reasoning: The virus spreads to skin through the innervating sensory pathway.

# **Application: New colitis after transplantation**

## **CLINICAL VIGNETTE**

A transplant recipient has severe colitis and a positive CMV tissue study.

**Why may a previously controlled virus become pathogenic?**

**Interpretation: Loss of cellular immune control**

Reasoning: CMV latency in hematopoietic cells can reactivate during immunosuppression.

# Application: Atypical lymphocytosis

## CLINICAL VIGNETTE

A young adult has fever, enlarged cervical nodes, splenomegaly, and many atypical peripheral lymphocytes.

**What does the atypical lymphocyte population mainly represent?**

**Interpretation: Activated cytotoxic T cells**

Reasoning: EBV infection of B cells elicits an expanded host CD8<sup>+</sup> response.

## **Four errors to avoid in interpreting latency**

- Calling latent viral DNA equivalent to continuous infectious virion production.
- Assuming the anatomical reservoir is identical to the active lesion site.
- Attributing every recurrent rash to the same herpesvirus without distribution/context.
- Equating virus detection with proof that it caused the presenting organ injury.

# **The unifying clinicopathologic model**

**A persistent genome becomes dangerous when productive infection resumes.**

- The affected cell type determines the reservoir.
- Tissue tropism, immune control, and reactivation determine clinical expression.
- Specific organisms differ sharply in their target organs and injury patterns.

# Primary reference and source scope

## Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Infectious Diseases

- **Core source:** Latent Infections (Herpesvirus Infections).
- **Contextual textbook sections:** Herpes Simplex Virus, Varicella-Zoster Virus, Cytomegalovirus, and Epstein-Barr Virus.
- The supplied Markdown text does not contain reusable diagnostic micrographs or the original printed chapter pages.