

Herpes Simplex Virus Infections

Oral and orofacial pathology

Primary disease • neural latency • recurrent mucocutaneous lesions • diagnostic morphology

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What the learner should recognize

- Identify the characteristic oral presentations of primary and recurrent HSV.
- Explain epithelial lytic infection, sensory-neuron latency, and reactivation.
- Recognize vesicular and cytopathic changes in affected epithelium.
- Distinguish typical HSV lesions from key oral mimics and high-risk disease.

The three common oral presentations

Childhood

Acute herpetic
gingivostomatitis

Adulthood

Acute or recurrent
pharyngitis

Immunocompromise

Chronic mucocutaneous HSV

HSV-1 and HSV-2: Overlapping syndromes

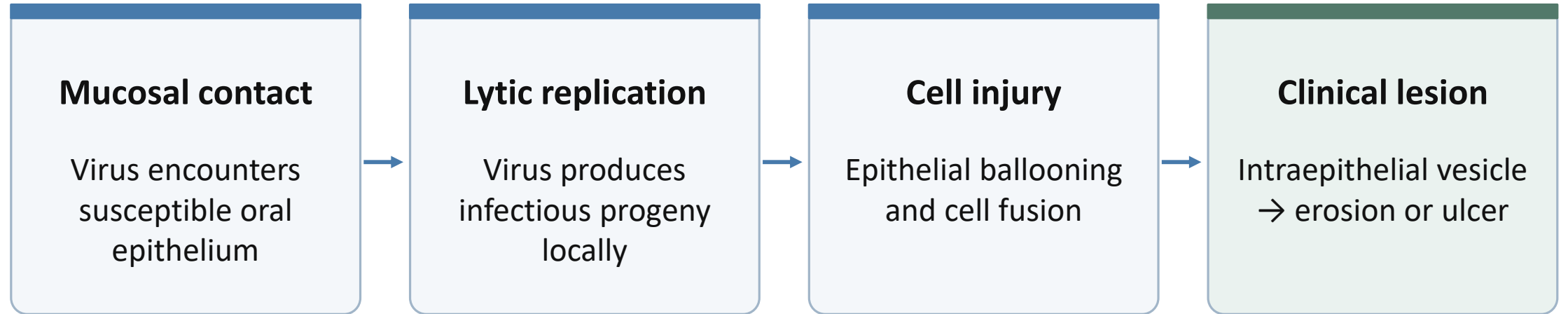
Dimension	HSV-1	HSV-2
Common association	Orofacial disease	Genital disease
Oral infection	Predominant orofacial type	Also possible
Shared properties	Primary infection, neuronal latency, recurrence	Primary infection, neuronal latency, recurrence
Type distinction	Antibody reactivity to type-specific glycoprotein G	Antibody reactivity to type-specific glycoprotein G

Oral disease is not exclusive to HSV-1

Anatomic site does not establish HSV serotype.

- Most orofacial infections involve HSV-1.
- Oral HSV-2 infections are documented.
- The two serotypes are genetically related and share pathogenic behavior.

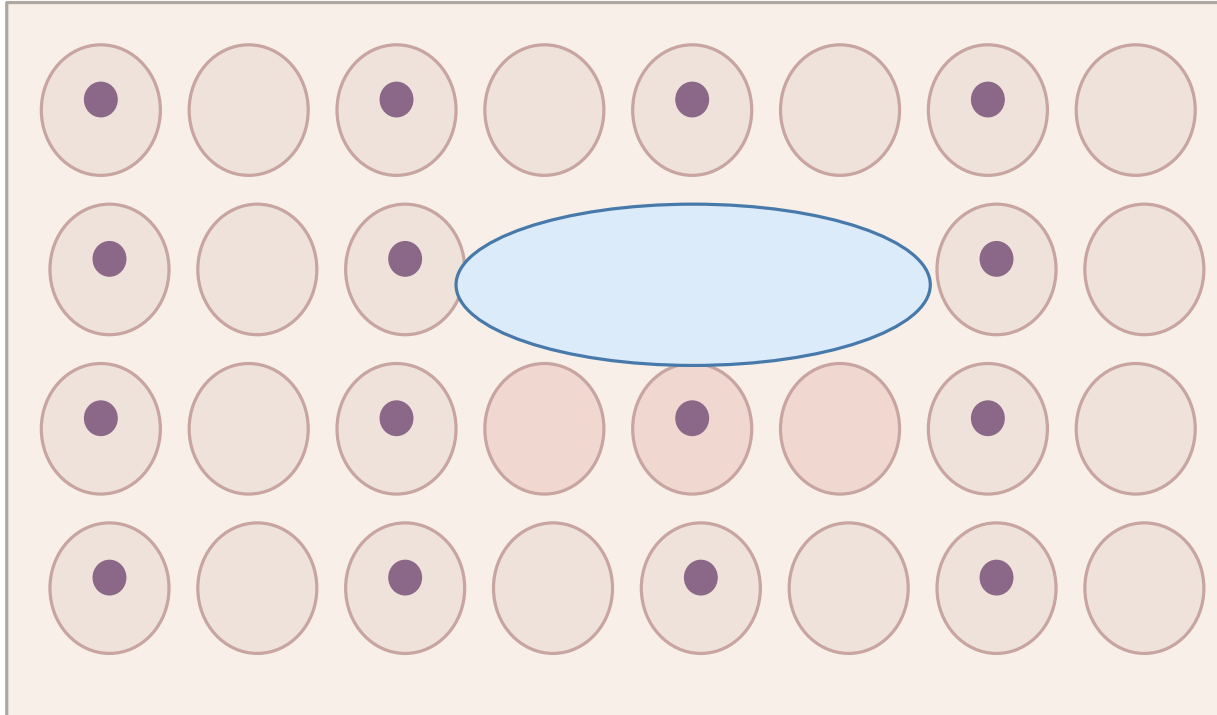
From exposure to a mucosal lesion



The oral epithelium is the first target

- Primary HSV replication occurs in skin or mucous membranes at the entry site.
- Epithelial infection generates infectious virions and locally destructive lesions.
- Vesicles reflect epithelial injury rather than a primary immune-complex eruption.
- Clinical disease may remain localized even though neural infection follows.

Epithelial cytolysis explains vesicle formation



Schematic • epithelial cell injury

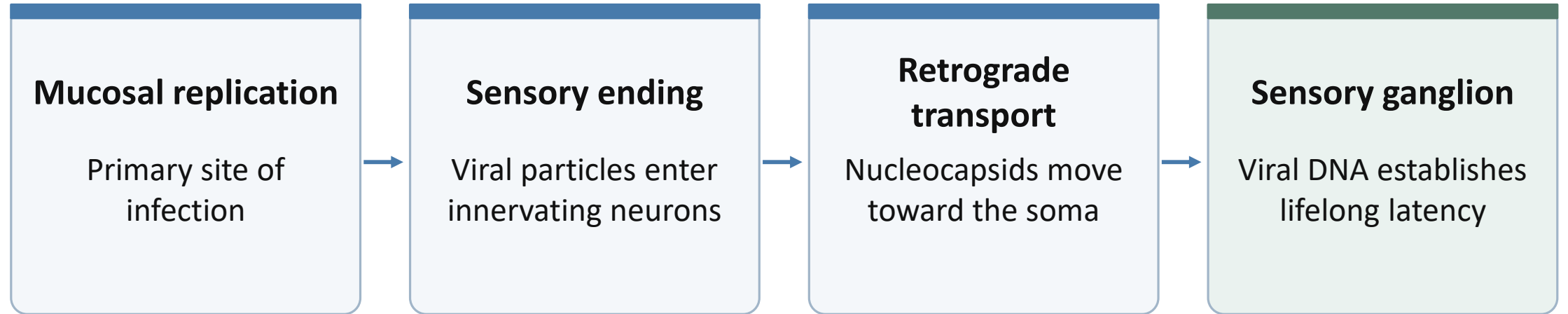
Morphologic interpretation

Ballooning degeneration distends infected keratinocytes.

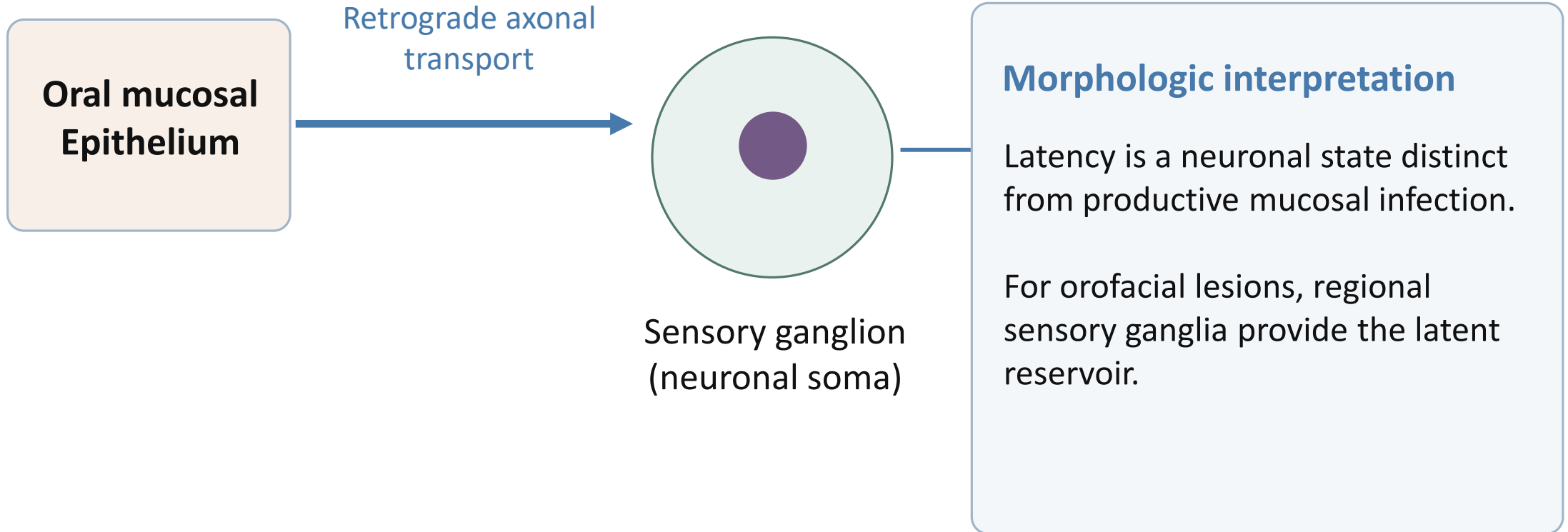
Intracellular and intercellular edema promotes clefting.

An intraepithelial fluid space becomes a visible vesicle.

HSV enters the sensory nervous system



Neural route: Mucosa to sensory ganglion

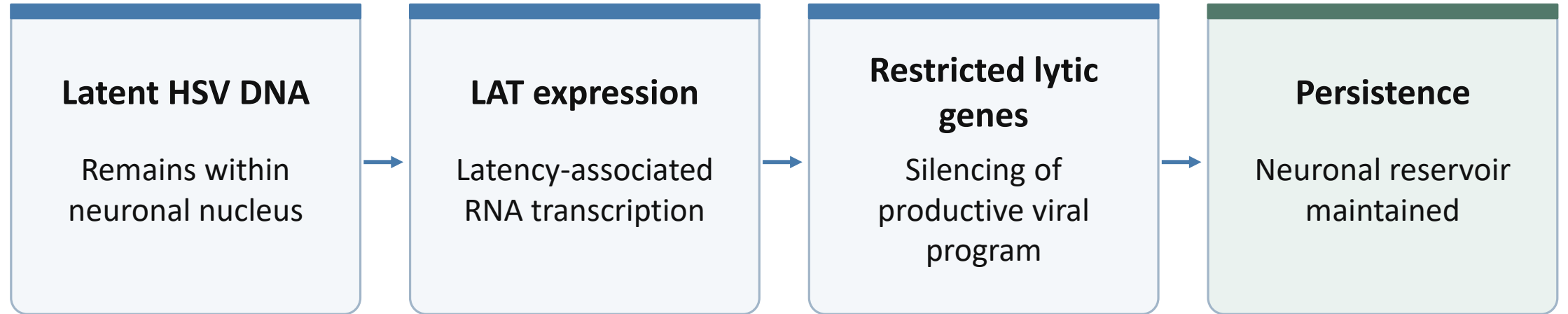


Schematic • not an anatomical micrograph

Latency is not eradication

- After the initial episode resolves, HSV DNA remains within neuronal nuclei.
- The genome is transcriptionally restricted rather than productively replicating.
- This persistence allows subsequent recurrence without a new exposure.
- Host immune control and the viral latency program coexist.

Latency-associated transcripts (LATs)

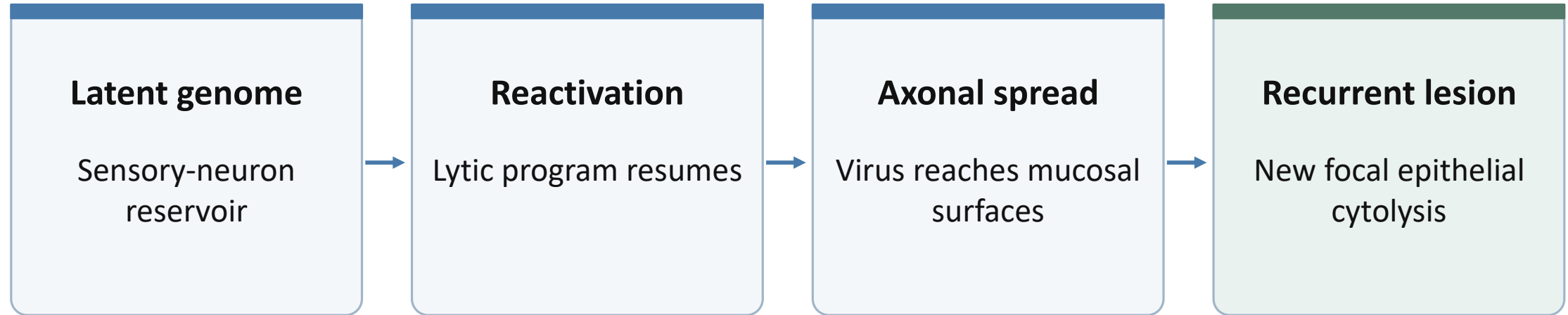


Anti-apoptotic, heterochromatin and microRNA mechanisms as possible LAT contributions.

Proposed functions of LATs

- LATs may reduce apoptosis of infected neurons.
- They may promote heterochromatin formation and silencing of lytic genes.
- LAT-derived microRNAs may suppress critical HSV lytic transcripts.
- These are mechanisms proposed, not deterministic clinical tests.

Reactivation reverses the direction of spread



Examples of reactivation triggers

Local injury

Trauma, ultraviolet exposure, temperature extremes

Intercurrent illness

Upper respiratory tract infection and related stress

Physiologic change

Pregnancy or menstruation

Host immunity

Immunosuppression favors more extensive recurrence

Reactivation may be symptomatic or silent

Viral reactivation does not always produce a visible vesicle.

- Recurrent HSV can spread from sensory neurons to epithelium repeatedly.
- Symptoms vary with local replication and host response.
- A previous infection explains renewed disease at familiar mucosal sites.

HSV survives despite immune responses

Cell-mediated recognition

HSV may interfere with MHC class I presentation.

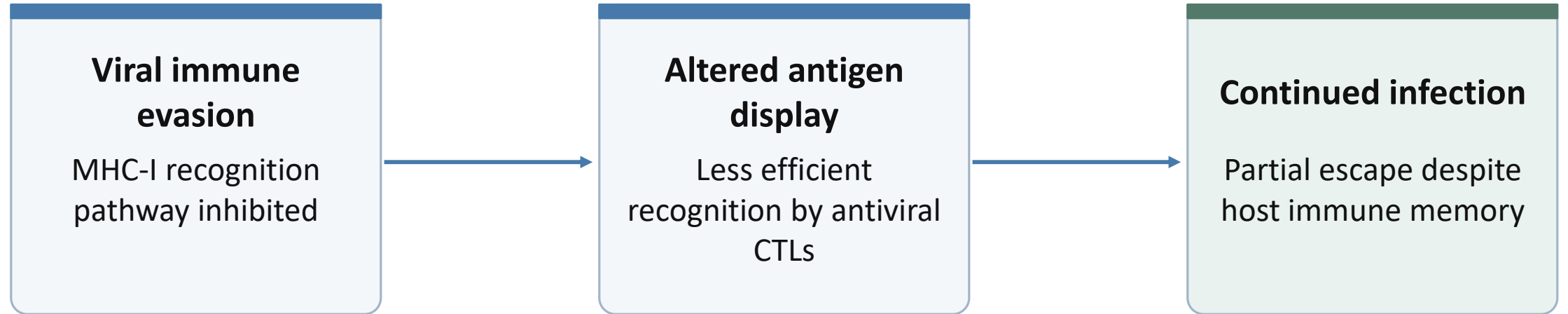
Antibody responses

Viral glycoprotein gE can bind the Fc domain of IgG.

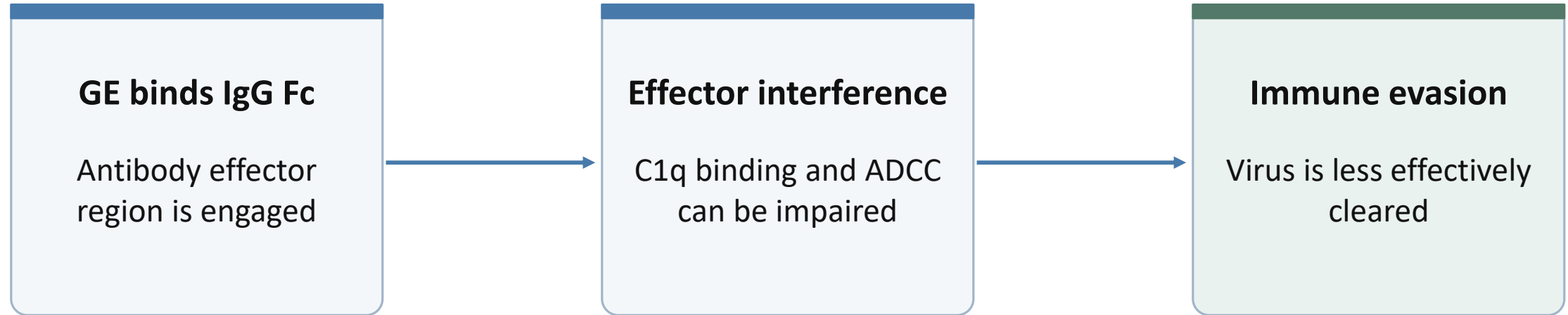
Complement pathways

Viral glycoprotein gC interacts with C3 and activation products.

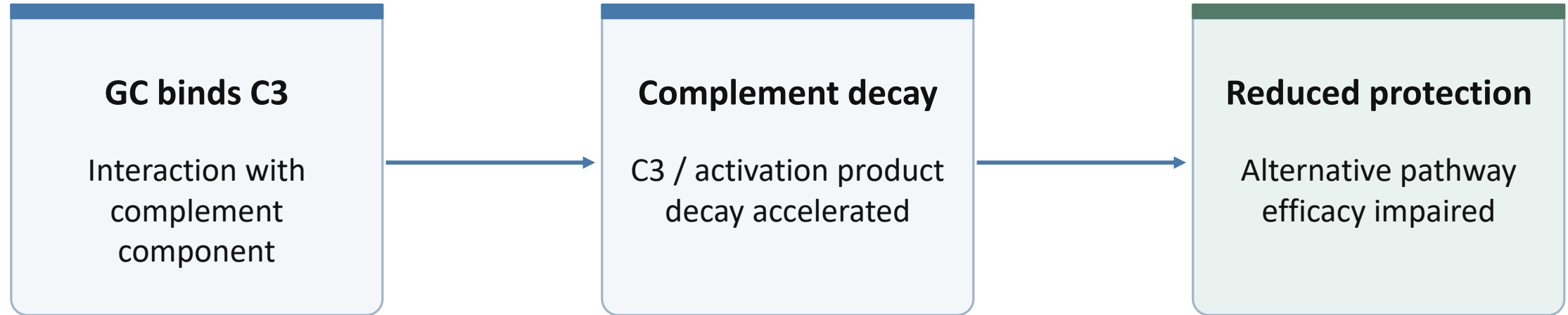
Reduced CD8+ T-cell recognition



Glycoprotein gE interferes with antibody function



Glycoprotein gC interferes with complement



Primary infection versus recurrence

Feature	Primary HSV infection	Recurrent HSV
Timing	First encounter with virus	Reactivation of persistent viral genome
Clinical expression	Often asymptomatic; may cause gingivostomatitis	Localized clustered vesicles
Anatomic pattern	Initial inoculation site	Same site or mucosa served by same ganglion
Underlying process	Mucosal replication plus neural seeding	Neural reactivation followed by mucosal infection

Childhood acquisition: The textbook pattern

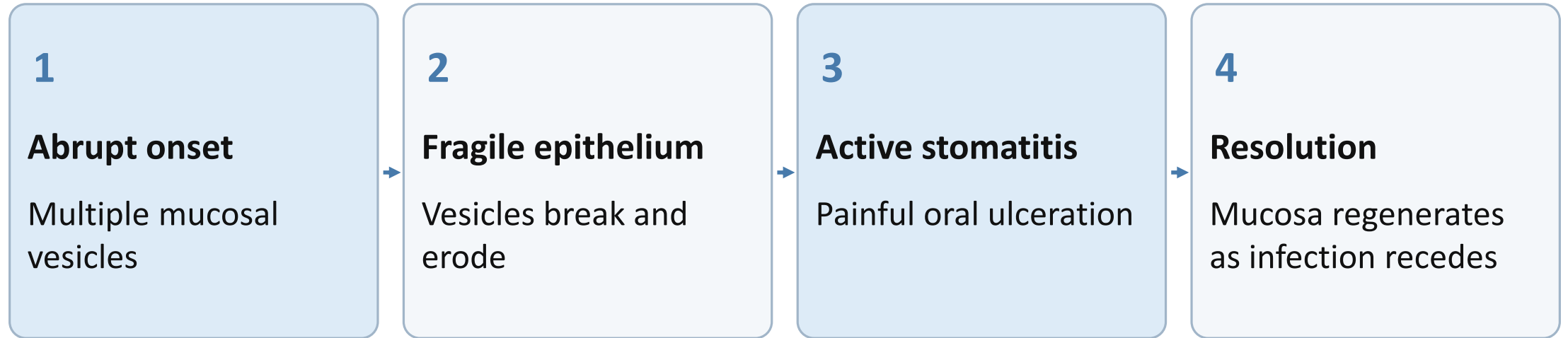
Primary oral HSV is particularly frequent between ages 2 and 4 years.

- A large proportion of childhood infections are asymptomatic.
- Symptomatic primary disease is acute herpetic gingivostomatitis.
- Age and clinical morphology should be interpreted together.

Why many primary infections go unrecognized

- Primary HSV may occur without a clinically obvious oral eruption.
- Absence of recalled gingivostomatitis does not exclude prior exposure.
- Latency can be established after subclinical mucosal replication.
- Future recurrence can be the first memorable manifestation.

Acute herpetic gingivostomatitis: Lesion evolution



Primary gingivostomatitis: Three tissue findings

Mucosa

Vesicles and ulcerations involving the oral surface

Gingiva

Diffuse inflammation contributes to gingivostomatitis

Regional nodes

Cervical lymphadenopathy may accompany the eruption

Systemic symptoms contextualize primary oral HSV

- Fever may accompany symptomatic childhood primary infection.
- Anorexia or reduced oral intake can result from painful lesions.
- Regional lymphadenopathy reflects local immune activation.
- Systemic findings are not mandatory for every infection.

The textbook's symptomatic-frequency statement

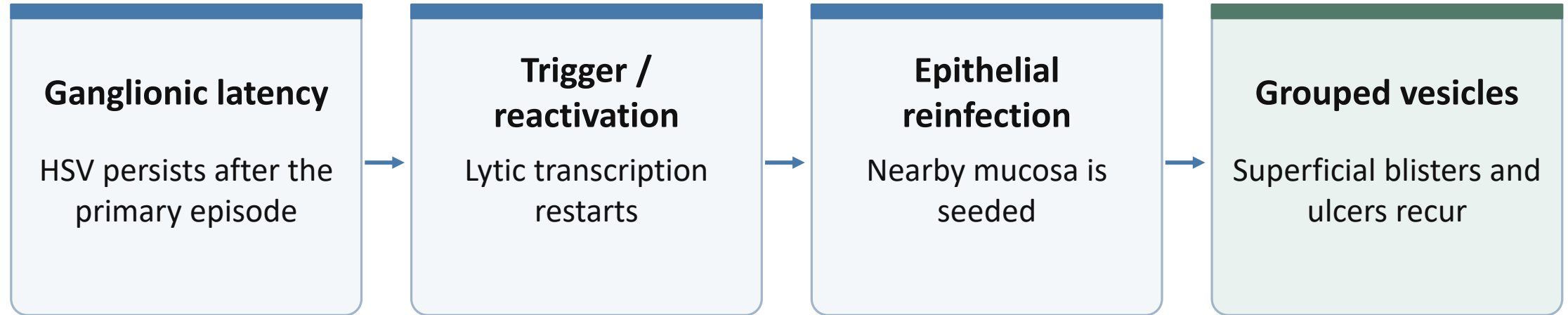
Up to 20% of childhood primary cases may present with acute gingivostomatitis.

- This statement refers to the source's pediatric presentation, not all HSV infections.
- Avoid applying this figure to adult recurrence or population-wide prevalence.
- The remaining infections are commonly clinically silent.

Adult oral HSV can involve the pharynx

- Acute herpetic pharyngitis is common in adults.
- The adult clinical phenotype differs from classic childhood gingivostomatitis.
- Acute pharyngeal involvement may recur.
- Etiology cannot be inferred from sore throat alone.

The pathogenesis of a recurrent oral episode

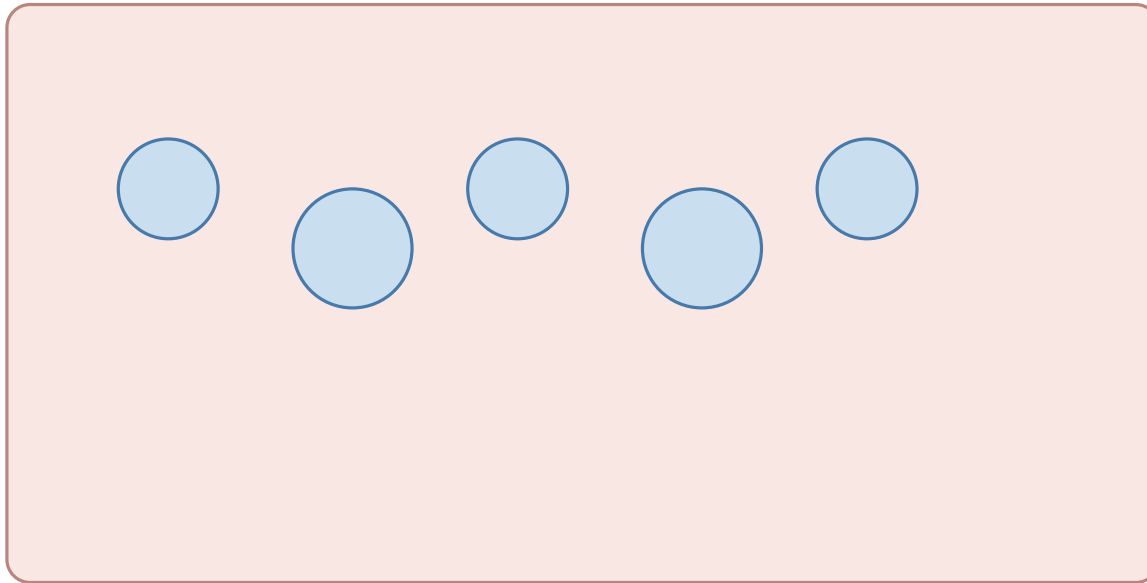


Anatomic recurrence follows neural territory

Recurrences favor the initial site or mucosa supplied by the same ganglion.

- Recurrence does not require a second exogenous exposure.
- A repeated distribution supports reactivation of latent infection.
- The precise mucosal point of recurrence can vary.

Small grouped vesicles are a major visual clue



*Grouped superficial vesicles
(schematic distribution; Not a patient photograph)*

Morphologic interpretation

Typical recurrent oral HSV vesicles measure about 1–3 mm.

They are clustered rather than solitary.

Rupture can replace a vesicular surface with shallow ulceration.

Common sites of recurrent orofacial HSV

Lips

Herpes labialis / “cold sores”

Nasal orifices

Periorificial vesicular clusters

Buccal mucosa

Recurrent focal mucosal eruption

Attached oral mucosa

Gingiva and hard palate

Herpes labialis: The classic recurrence

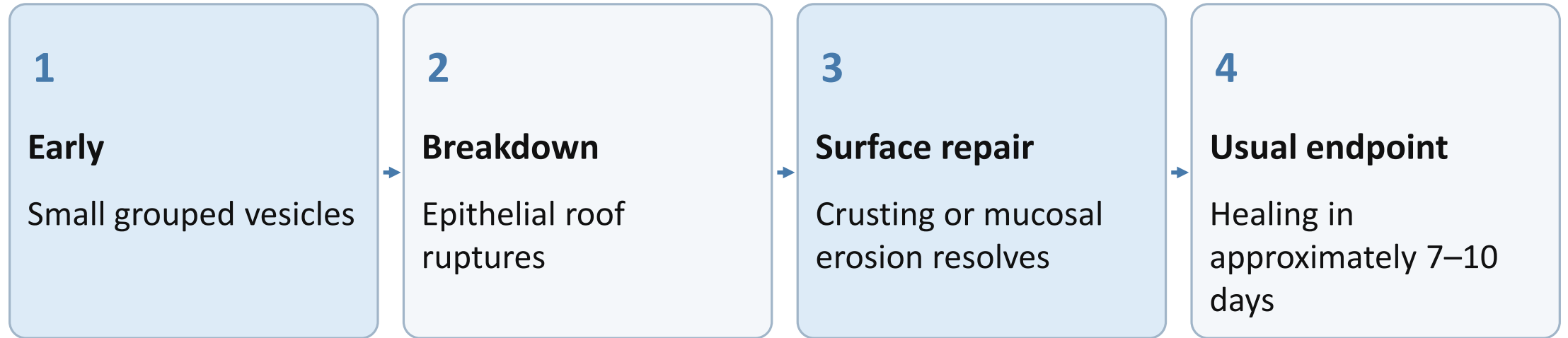
Clusters of small vesicles involve the labial or perioral surface.

- Lip lesions may rupture and subsequently crust.
- Oral/facial HSV is often bilateral or not dermatomally restricted.
- This pattern contrasts with zoster distribution.

Recurrent disease may involve multiple oral zones

- The buccal mucosa, gingiva and hard palate are documented sites.
- The nasal orifices are another frequent orofacial site.
- A typical recurrent outbreak remains a clustered, superficial epithelial process.
- The lesion site is informative but not uniquely diagnostic.

Typical recurrent lesion: Visible natural history



An unusually persistent lesion changes the risk assessment

HSV lesions may remain active longer in immunocompromised hosts.

- Prolonged ulcers should not automatically be labeled benign recurrent herpes.
- Persistent HSV can require systemic antiviral treatment.
- The clinical setting is as important as morphology.

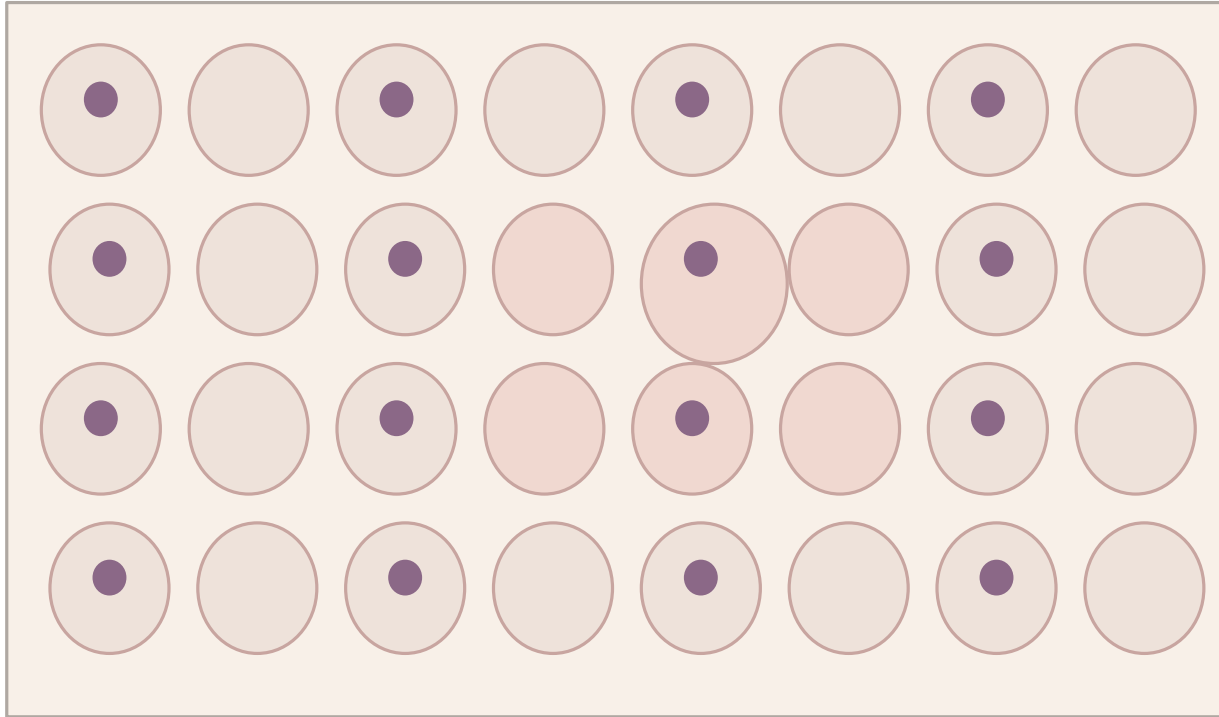
Immune status modifies the phenotype

Feature	Immunocompetent host	Immunocompromised host
Typical course	Self-limited oral episodes	Prolonged or chronic mucocutaneous lesions
Viral control	Cellular immunity restricts spread	Control may be impaired
Major concern	Local pain and recurrence	Persistent disease or dissemination
Clinical implication	Recognize the usual recurrent pattern	Assess for severe or disseminated involvement

Clinical settings that favor severe HSV

- HIV-related impairment of cellular immunity may permit unusually severe infection.
- Chemotherapy and other immunosuppressive states increase vulnerability.
- Neonates are also at risk of disseminated infection.
- Disseminated disease lies beyond uncomplicated oral herpes.

How ballooning degeneration produces a blister



Schematic • epithelial cell injury

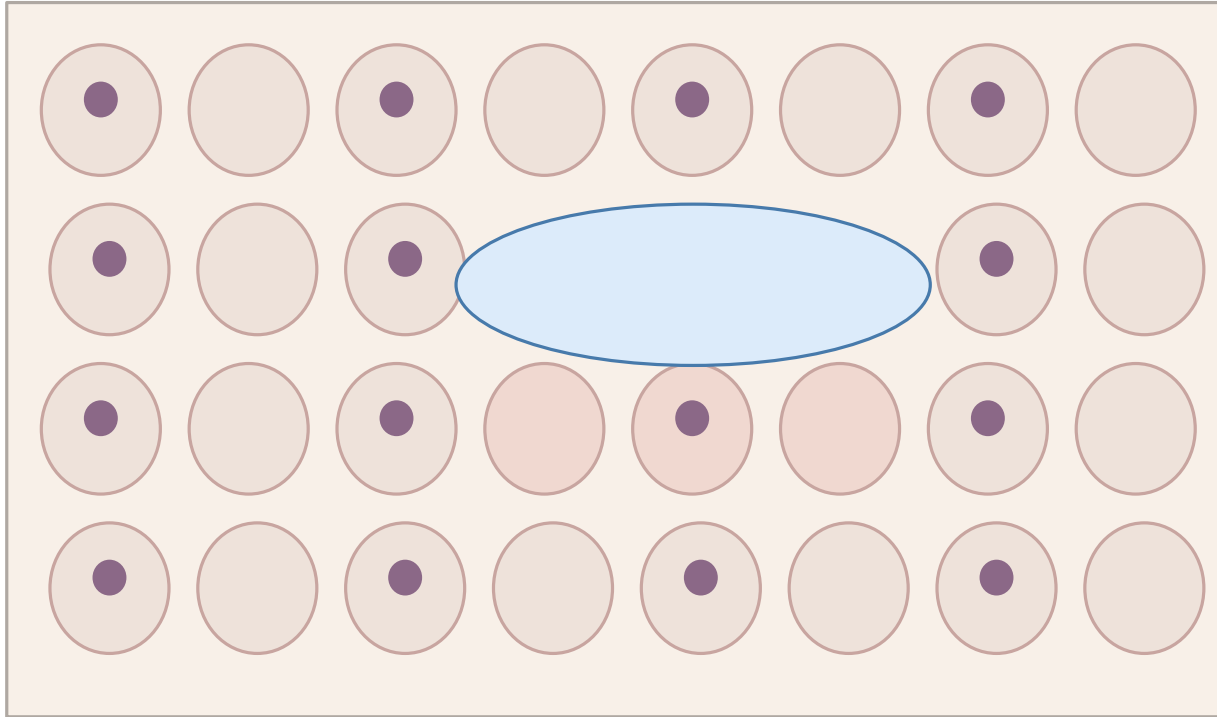
Morphologic interpretation

Cytolysis causes swollen epithelial cells.

Edema and intercellular separation generate a cleft.

Coalescing spaces create an intraepithelial vesicle.

HSV vesicle: Tissue-level architecture



Schematic • epithelial cell injury

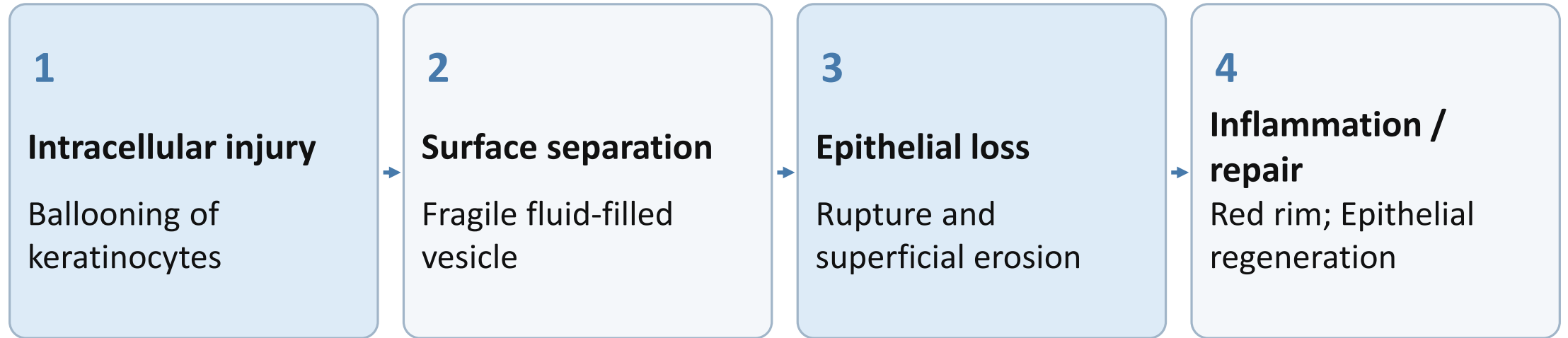
Morphologic interpretation

The blister lies within the stratified squamous epithelium.

Injured keratinocytes can remain near the vesicle margin.

Inflammatory cells appear as the lesion evolves.

Vesicle rupture creates a shallow ulcer

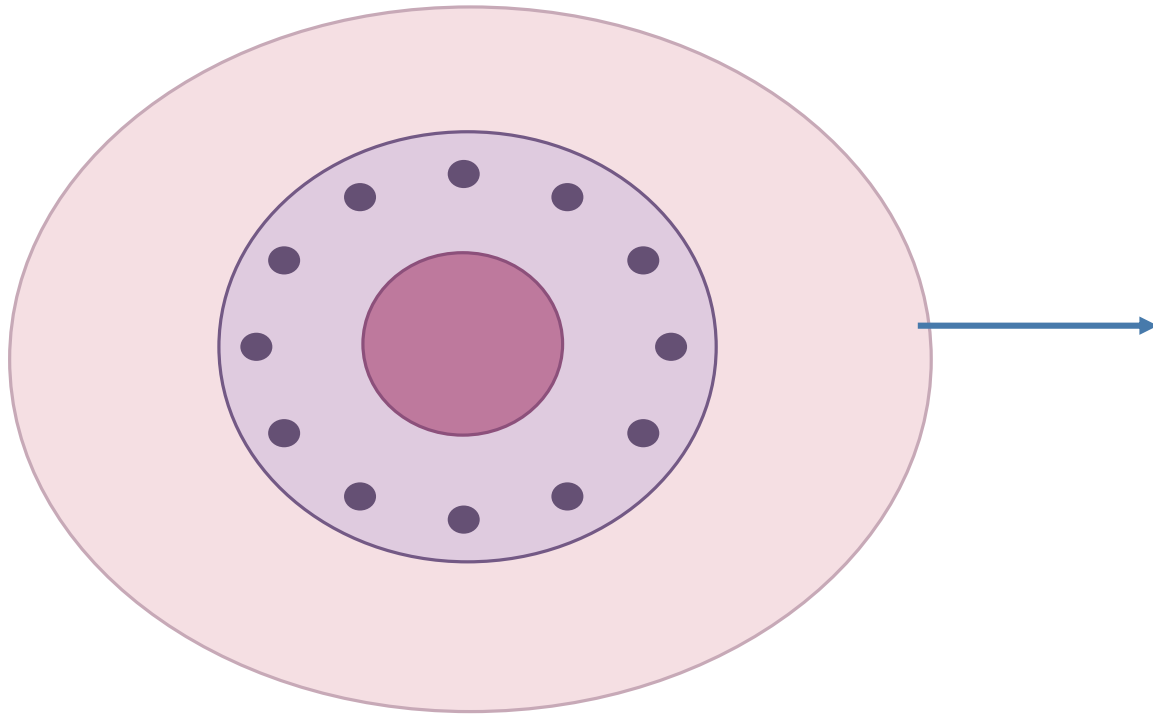


Cowdry type A inclusions: Nuclear HSV effect

Characteristic infected cells have large pink-to-purple intranuclear inclusions.

- Inclusions represent viral proteins and virions during assembly.
- Host chromatin is pushed toward the nuclear periphery.
- Recognition is a cytopathic clue, not an HSV serotype test.

Cowdry type A inclusion: Conceptual cell



Intranuclear inclusion

Morphologic interpretation

Peripheral chromatin forms a dense rim.

An inclusion lies within the nucleus, sometimes with surrounding clearing.

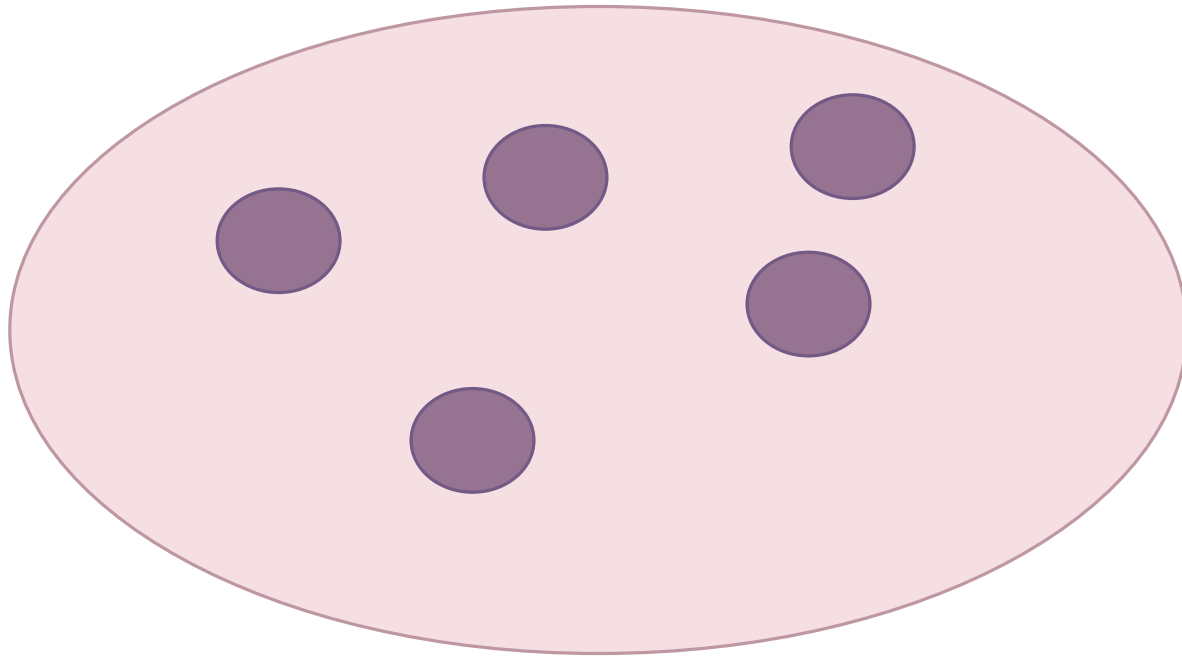
Appearance here is explanatory artwork, not an H&E specimen.

Cell fusion creates multinucleated syncytia

HSV can produce multiple nuclei inside a single infected epithelial cell.

- Syncytia result from virus-mediated cell fusion.
- Infected nuclei may also contain herpetic inclusions.
- Multinucleation and inclusions are complementary morphologic observations.

HSV syncytium: Conceptual cell fusion



*A single fused cell with several nuclei
(schematic, not microscopic evidence)*

Morphologic interpretation

Adjacent infected keratinocytes fuse into a multinucleated polykaryon.

A multinucleated cell may be seen in vesicle material.

Such changes support a herpesvirus cytopathic pattern.

Cytology can show herpetic cytopathic effect

- Active vesicular material can contain infected epithelial cells.
- Multinucleated cells and intranuclear inclusions are diagnostic clues.
- Demonstration of multinucleate cells on a Tzanck preparation.
- Morphology must be interpreted with lesion distribution and clinical findings.

What a Tzanck preparation does and does not show

Can demonstrate	Cannot establish alone
Multinucleated epithelial cells	HSV-1 versus HSV-2 serotype
Herpesvirus-type cytopathic morphology	A definite distinction between HSV and VZV
Rapid morphologic clue from a vesicle	Extent of latent infection in sensory ganglia

A late biopsy may no longer show an intact blister

- HSV vesicles rupture rapidly, exposing superficial ulcerated mucosa.
- Biopsied lesions may contain desquamated epithelium and acute inflammation.
- Infected epithelial cells at the margin may preserve cytopathic changes.
- Specimen timing can influence morphologic yield.

HSV versus recurrent aphthous ulceration

Discriminator	Herpes simplex	Aphthous ulcers
Initial surface	Clusters of vesicles	Shallow ulcers with exudative surface
Distribution	Labial / gingival / palatal and other oral sites	Variable oral mucosal sites
Etiology	Persistent latent neurotropic virus	Cause uncertain in Robbins
Course	Recurrent, often same neural territory	Often recurrent; not a herpesvirus infection

HSV versus oral candidiasis

Discriminator	Herpetic lesion	Oral thrush
Common surface	Vesicles or superficial ulcers	Gray-white pseudomembrane
Key tissue change	Viral epithelial cytolysis	Fungal organisms in surface exudate
Removal of surface	Fragile blister / erosion	Pseudomembrane readily scraped
Shared context	Can worsen with immunosuppression	Commonly promoted by immunosuppression

HSV versus herpes zoster

Discriminator	HSV recurrence	Reactivated VZV / zoster
Cutaneous pattern	Often periorificial; not restricted to dermatome	Characteristic segmental / dermatomal eruption
Recurrence	Repeated episodes possible	Less frequent in immunocompetent persons
Neural correlate	Sensory-ganglion reservoir	Dorsal root or cranial sensory ganglia
Cytology	Herpesvirus inclusions and multinucleation	Similar herpesvirus cytopathic effect

Other oral infections in the differential

Enteroviruses

Herpangina and hand-foot-and-mouth disease may involve the oral region.

EBV

Hairy leukoplakia produces white lateral tongue plaques, not vesicular clusters.

Cytomegalovirus

Included among oral/head-and-neck viral infections.

Rubeola / measles

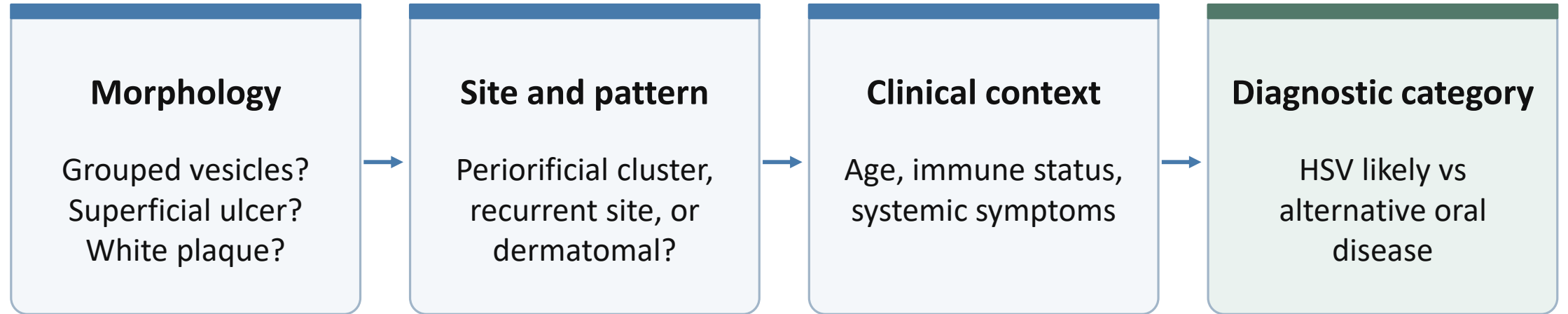
A separate viral disease that may affect the oral cavity.

Oral hairy leukoplakia is not recurrent oral HSV

EBV-associated hairy leukoplakia typically forms white lateral-tongue plaques.

- The white plaque generally cannot be scraped off.
- HSV recurrence instead produces vesicles that ulcerate.
- The setting of immunosuppression can occur in both entities.

Reasoning from a painful oral lesion



Anatomy plus morphology is stronger than either alone

Interpret the visible lesion in its clinical and neural context.

- Grouped small vesicles at a recurrent site strongly support HSV.
- A solitary shallow fibrin-covered ulcer raises other possibilities.
- A persistent atypical ulcer in an immunocompromised host requires careful evaluation.

Type-specific serology addresses a different question

Morphology	Type-specific antibody assessment
Characterizes local cytopathic changes	Uses type-specific glycoprotein G antigenicity
Can support a herpesvirus-induced lesion	Can distinguish immunologic recognition of HSV-1 / HSV-2
Does not reliably separate HSV types	Does not itself localize the active oral lesion

Two mechanisms of HSV keratitis

Corneal epithelial keratitis	Corneal stromal keratitis
Direct virus-induced epithelial cytolysis	Immune-mediated stromal injury
Loss of superficial epithelial integrity	Mononuclear inflammatory infiltration
Reflects active epithelial infection	Can cause vessels, opacity and scarring

Ocular extension matters clinically

- Recurrent HSV can cause corneal ulcerations.
- Corneal epithelial damage can be directly viral.
- Stromal disease can instead reflect a damaging immune response.
- Corneal scarring and loss of transparency threaten vision.

Herpetic whitlow: A nonoral manifestation

HSV can cause painful, erythematous lesions of the fingers or palm.

- This manifestation occurs in infants and occasionally after occupational exposure.
- The same epithelial cytopathic process operates outside the oral mucosa.
- It is a clinicopathologic extension, not the central topic of this lecture.

Dissemination is not routine recurrent herpes

- Immunocompromise can permit skin and visceral dissemination.
- Robbins documents esophagitis, bronchopneumonia and hepatitis.
- Necrotizing pneumonia or hepatitis represents severe organ involvement.
- Suspicion rises when mucocutaneous disease is unusually persistent or widespread.

Local oral HSV versus visceral HSV

Uncomplicated orofacial episode	Severe systemic infection
Grouped vesicles and shallow erosions	Potential visceral organ necrosis
Usually self-limited in intact immunity	Often associated with immunosuppression
Local mucosal epithelial injury	May involve esophagus, lung, liver or CNS

Neurologic HSV disease: A boundary reminder

- Neuronal latency is common; Encephalitis is a separate severe manifestation.
- HSV-1 encephalitis preferentially involves the temporal and orbital-frontal regions.
- Defects in TLR3 signaling are associated with susceptibility.
- Oral recurrence alone is not evidence of encephalitis.

Case 1: Febrile child with oral erosions

Clinical vignette

A 3-year-old has abrupt oral vesicles progressing to painful erosions, fever, reduced intake, and enlarged cervical nodes.

What presentation best unifies the age, morphology and systemic symptoms?

What local cellular event initially produces the vesicles?

Case 1 interpretation: Primary gingivostomatitis

A first symptomatic oral HSV episode is the most coherent explanation.

- Childhood primary disease can present with acute gingivostomatitis.
- Lytic epithelial infection produces fragile intraepithelial blisters.
- Fever and regional lymphadenopathy are recognized accompanying features.

Case 2: Recurrent lip vesicles

Clinical vignette

An otherwise healthy adult describes repeated clusters of tiny vesicles at nearly the same lip site, healing after about a week.

Does repeated disease imply repeated new HSV acquisition?

What explains the similar site and short natural history?

Case 2 interpretation: Recurrent herpes labialis

Reactivation from a regional sensory-ganglion reservoir explains recurrence.

- Small clustered vesicles on the lip are characteristic.
- Relapse near the previous inoculation site reflects related neural innervation.
- The 7–10-day course is consistent with uncomplicated recurrence.

Case 3: Prolonged ulceration in immunosuppression

Clinical vignette

An adult receiving immunosuppressive therapy develops persistent orofacial ulceration that does not follow a brief self-limited course.

What makes this scenario different from usual herpes labialis?

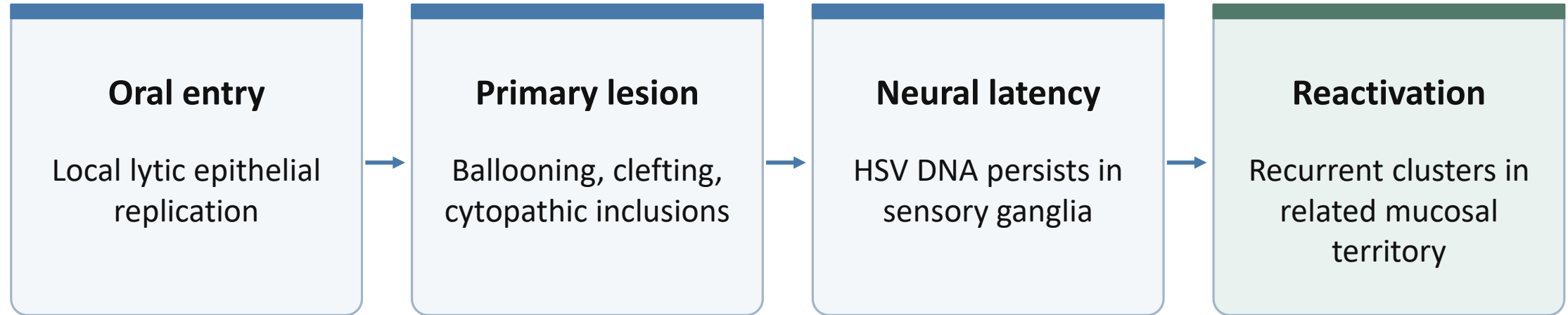
Which major complication category deserves particular consideration?

Case 3 interpretation: Complicated mucocutaneous HSV

Chronic or extensive HSV is a recognized presentation in immunocompromised hosts.

- Persistence should trigger careful clinical and etiologic reassessment.
- Severe disease may require systemic antiviral therapy.
- Disseminated or visceral HSV is a clinically important possibility.

Connecting mechanisms to observed pathology



Four errors worth avoiding

Serotype inference

Do not assume every oral HSV lesion must be HSV-1.

Pattern inference

Do not call a solitary aphthous ulcer recurrent HSV without support.

Microscopy inference

Tzanck morphology is not specific HSV typing.

Severity inference

Do not dismiss chronic ulceration in immunocompromised hosts.

Integrated clinicopathologic conclusions

- HSV causes primary mucosal injury followed by sensory-neuron latency.
- Reactivation generates clustered small periorificial or oral vesicles.
- Ballooning, intranuclear inclusions, and multinucleation explain the morphology.
- Immune status governs persistence and risk of organ involvement.
- Clinical distribution and lesion architecture drive the oral differential.

Textbook source map

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 16: Head and Neck, oral HSV section, p. 666–667.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 8: Infectious Diseases, HSV section, pp. 321–322.

Adjacent Chapter 16 sections: aphthous ulcers, oral candidiasis, and hairy leukoplakia.

Chapter 22: HSV cytopathic changes in genital-tract specimens (limited supporting comparison).