

# Herpes Simplex Virus Type 1

Necrotizing encephalitis · neuropathology · clinical interpretation

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## Learning outcomes: Mechanistic and diagnostic reasoning

- Trace HSV-1 from mucosal replication through neuronal latency and CNS injury.
- Relate temporal and orbitofrontal involvement to the neurological presentation.
- Recognize necrotizing, often hemorrhagic encephalitis and its microscopic correlates.
- Integrate clinical recognition, CSF molecular testing, and urgent antiviral treatment.

# HSV-1: Two linked but distinct disease contexts

## Primary and recurrent infection

Replication at mucosal or skin surfaces

Vesicular lesions and mucosal shedding

Neuronal latency persists after recovery

## Central nervous system disease

Invasion of brain parenchyma

Necrotizing, often hemorrhagic  
encephalitis

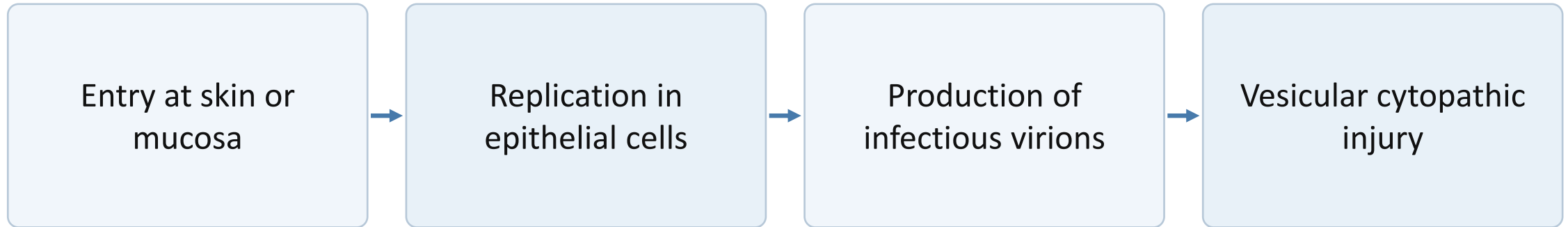
Acute neurologic dysfunction

*Most HSV infections do not lead to encephalitis.*

# Alpha-herpesvirus biology relevant to pathology

- HSV-1 and HSV-2 are closely related human alpha-herpesviruses.
- Their genomes consist of double-stranded DNA.
- Alpha-herpesviruses replicate in epithelial cells and establish latency in postmitotic neurons.
- The ability to alternate between lytic infection and latency is central to recurrence.

## Mucosal entry creates an initial site of replication

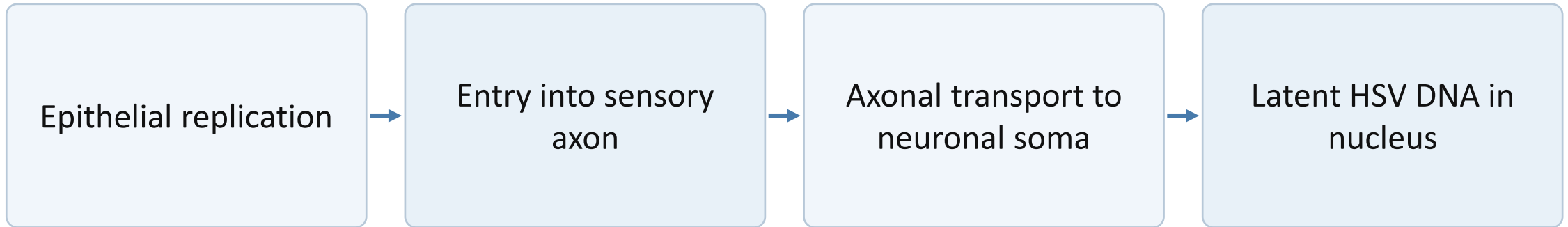


HSV establishes infection at the site of entry before neuronal latency.

## Primary mucocutaneous lesions reflect direct cytolysis

- Intraepithelial vesicles result from ballooning degeneration and edema of epidermal cells.
- Fragile vesicles can rupture, crust, or form superficial ulcerations.
- Perioral cold sores commonly involve the skin around the lips and nose.
- Mucocutaneous morphology differs from parenchymal brain necrosis.

## Sensory neurons establish the reservoir for latency



Movement toward sensory ganglion neuronal cell bodies follows peripheral replication.

## Latency: Persistence without infectious virus production

- Latency means viral genomes persist in cells without generating infectious virions.
- The neuronal cell nucleus maintains HSV DNA after mucosal disease resolves.
- Latency is distinct from ongoing productive lytic replication.
- Reactivation can later generate infectious virus despite pre-existing host immunity.

# Lytic replication versus latency

## Lytic state

Viral genes expressed in a productive program

Infectious virions are released

Tissue cytopathic changes may develop

## Latent state

HSV DNA persists in the neuronal nucleus

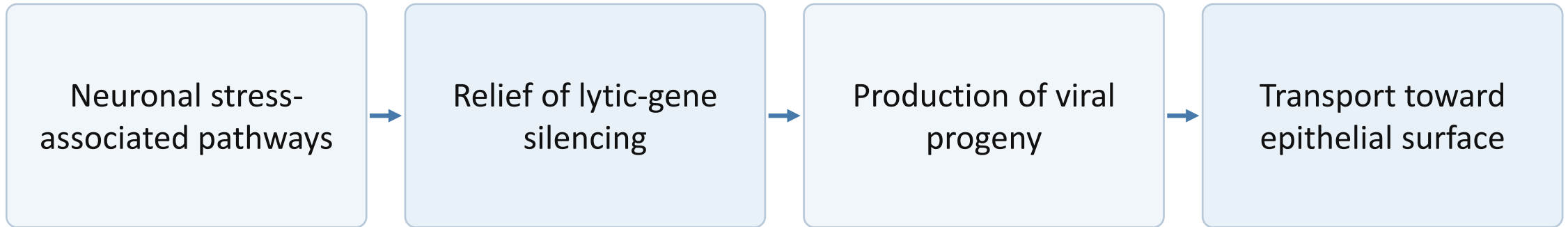
Latency-associated transcripts predominate

No infectious virus is produced

## Latency-associated transcripts (LATs)

- During latency, transcription is restricted largely to latency-associated RNAs.
- LATs may favor neuronal survival by reducing apoptosis.
- They may help silence lytic genes through chromatin modifications.
- LAT-derived microRNAs may downregulate viral gene expression; These are proposed mechanisms.

## Reactivation reverses the latent state



Reactivation may produce symptoms—or asymptomatic viral shedding.

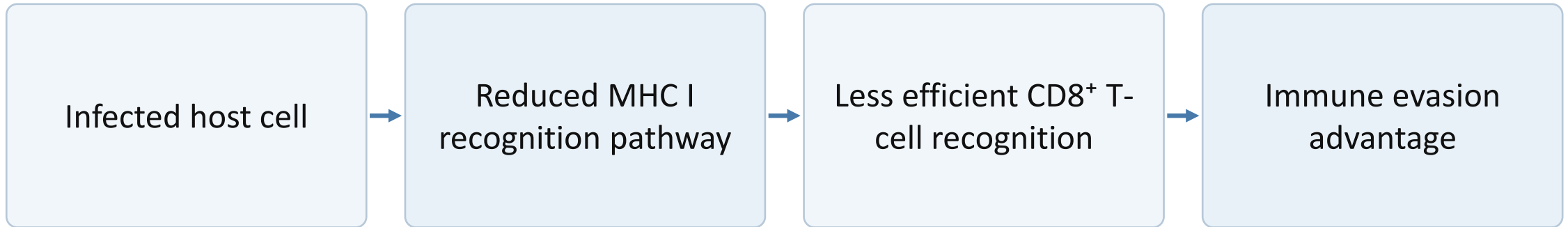
## Clinical recurrence does not require repeated new exposure

- Primary HSV infection often resolves in immunocompetent individuals.
- Persistent neuronal HSV DNA provides a source for later reactivation.
- Repeated lesions can arise from reactivation of the same latent infection.
- A history of recurrent cold sores cannot be used to establish or exclude encephalitis.

# Immune escape helps HSV persist in an immune host

- HSV has evolved several strategies to diminish immune recognition and antiviral effector pathways.
- Such evasion helps explain reactivation despite prior adaptive immunity.
- Three examples involve MHC class I, IgG Fc interactions, and complement.
- These are separate mechanisms: Avoid collapsing them into a single pathway.

# MHC class I interference weakens antiviral CTL recognition



CD8<sup>+</sup> cytotoxic T cells usually identify infected cells via peptide–MHC I complexes.

# HSV glycoprotein gE interferes with antibody effector function

HSV gE binds IgG Fc region



Interference with effector  
access



Reduced C1q / Fc-dependent  
actions

Binding Fc can limit useful functions of already bound antiviral antibodies.

# HSV glycoprotein gC targets complement

HSV gC interacts with C3



Accelerated loss of active C3  
products



Reduced alternative-pathway  
function

This is distinct from the Fc-binding mechanism involving gE.

# Immune evasion and tissue destruction can coexist

## Immune evasion

Latency and recurrence despite immunity

MHC class I, antibody and complement interference

## Immune-mediated consequences

Inflammatory recruitment into infected tissue

Parenchymal injury alongside viral cytopathic effects

*Neither “direct viral damage” nor “inflammation” alone explains all lesions.*

## Host TLR3 signaling is a susceptibility factor

- Inherited defects in TLR3 or components of its signaling pathway increase susceptibility to HSV encephalitis.
- TLR3 participates in innate antiviral recognition of viral RNA.
- A predisposition to CNS infection does not imply every patient has a detectable inherited defect.
- This is a mechanistic risk association, not a routine tissue diagnostic biomarker.

# HSV-1 encephalitis is a parenchymal syndrome

## Meningitis

Predominantly meningeal inflammation

Clinical meningeal syndrome possible without major parenchymal dysfunction

## Encephalitis

Infection and injury within brain tissue

Behavior, memory, consciousness or seizures reflect parenchymal dysfunction

*Viral encephalitis commonly coexists with meningeal inflammation (meningoencephalitis).*

## HSV-1 is a major cause of sporadic fatal encephalitis

- HSV-1 as a major cause of fatal sporadic encephalitis in the United States.
- The key teaching signature is limbic/temporal and orbitofrontal involvement.
- Untreated destructive infection can lead to extensive parenchymal necrosis.
- Antiviral treatment has substantially reduced mortality.

# Anatomic predilection is a central diagnostic clue

*Conceptual regions of predilection — schematic, not to anatomical scale*

Anterior / orbital frontal  
cortex

Inferior and medial temporal  
regions

Additional cingulate  
involvement in illustrated  
severe cases

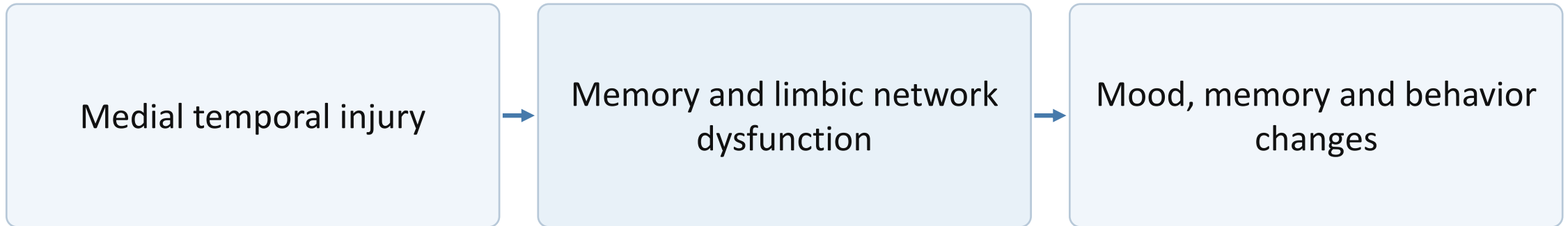
**Necrotizing inflammation ± hemorrhage**

*Distribution is highly suggestive but is not a pathogen-specific diagnostic test.*

## Typical involvement begins in specific cerebral regions

- The inferior and medial temporal lobes are most prominently involved.
- The orbital gyri of the frontal lobes are another classic site.
- Gross examples may extend to anterior temporal, inferior frontal and cingulate regions.
- Regional predilection is useful but not a standalone etiologic diagnosis.

# Anatomy predicts the clinical pattern



The regional clinicopathologic relationship helps distinguish encephalitis from isolated meningitis.

## Mood and behavior changes can be presenting features

- Altered mood and behavior as typical clinical manifestations.
- Orbitofrontal and limbic network dysfunction provides a plausible anatomic explanation.
- Behavioral disturbance can precede recognition of an infectious CNS process.
- Diagnostic reasoning should integrate behavior changes with new neurologic dysfunction.

## Memory impairment points toward temporal-limbic injury

- Memory alteration is among the typical presenting features.
- Medial temporal injury disrupts circuits important for memory formation.
- Memory deficit is a localizing clue rather than a pathogen-specific sign.
- The combination with evolving encephalopathy heightens suspicion for HSV encephalitis.

## Seizures signal irritable, damaged cerebral tissue

- Seizures are listed among manifestations of the more protracted HSV-1 presentation.
- Necrotizing inflammation and neuronal dysfunction create a substrate for epileptic activity.
- Seizures may coexist with weakness, lethargy or behavioral disturbance.
- An encephalitic syndrome warrants attention to nonconvulsive seizures.

## Subacute HSV-1 encephalitis is recognized

- Some cases evolve over a prolonged interval rather than a rapidly fulminant course.
- Weakness, lethargy, ataxia and seizures may unfold over four to six weeks.
- Slowly evolving cases may show more diffuse brain involvement.
- A prolonged history does not exclude infection with HSV-1.

# Two clinically described tempos of HSV-1 encephalitis

*Course describes clinical evolution; Time windows are not diagnostic thresholds*

Acute encephalitic presentation  
Behavior · memory · mood



Subacute course  
Weakness · lethargy · ataxia · seizures

Some subacute cases evolve over approximately 4–6 weeks

*A prolonged course may correlate with more diffuse parenchymal involvement.*

## Prior herpetic lesions are absent in most encephalitis cases

- That only about 10% have a history of prior herpetic infection.
- A negative history of cold sores does not argue strongly against HSV-1 encephalitis.
- Mucocutaneous symptoms are not required for the brain infection to be clinically evident.
- Avoid anchoring on the presence or absence of vesicles.

## Age distribution described

- The Chapter 28 text states that HSV-1 encephalitis occurs most commonly in children and young adults.
- This wording describes the cited textbook—not an age-based rule-out criterion.
- Neither older age nor immunocompetence excludes HSV encephalitis.
- Age should be integrated with phenotype, localization and laboratory results.

# Encephalitis and ordinary cold sores are not equivalent

## Common mucocutaneous infection

Epithelial vesiculation and ulceration

Often self-limited locally

Latent reservoir remains

## Rare severe neurologic manifestation

Direct injury within brain parenchyma

Temporal/orbitofrontal necrosis

Urgent diagnostic and treatment response

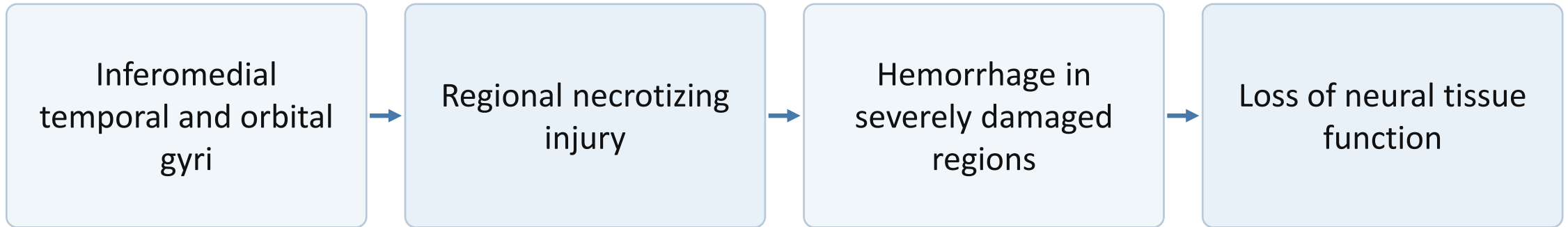
# Gross neuropathology: Necrotizing encephalitis

- The lesion is destructive: Involved parenchyma undergoes tissue necrosis.
- Damage predominates in medial/inferior temporal and orbitofrontal regions.
- Necrosis corresponds clinically to acute neuronal dysfunction.
- The distribution is more informative than simply calling the brain “inflamed.”

## Hemorrhage is a frequent, not obligatory, component

- HSV-1 encephalitis as often hemorrhagic in severely affected regions.
- Hemorrhage accompanies destructive parenchymal inflammation and vascular injury.
- Absence of gross hemorrhage does not exclude HSV infection.
- Never infer a specific pathogen from hemorrhage alone.

# Gross damage links topography to neurologic loss

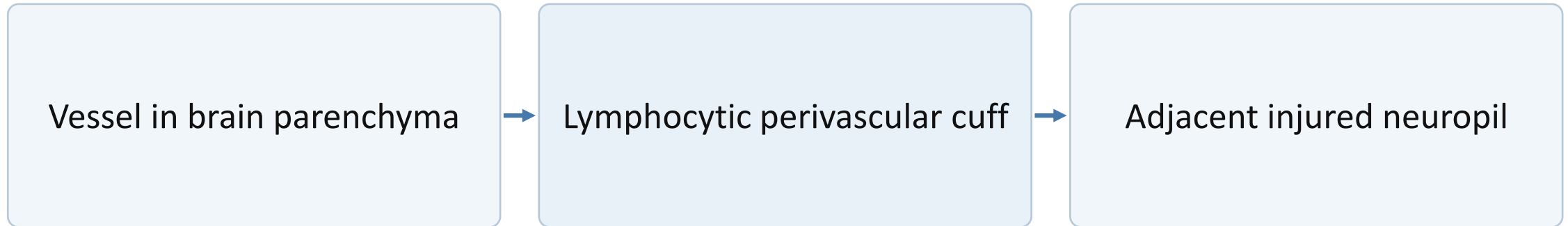


This sequence summarizes features of the lesion; Hemorrhage is common but not obligatory.

## Microscopic pattern: Inflammation around vessels

- Perivascular inflammatory infiltrates are usually found in acute HSV-1 encephalitis.
- Lymphocyte-rich perivascular cuffs are a common feature of viral encephalitis in general.
- Cuffing demonstrates inflammation but cannot establish HSV-1 by itself.
- Interpret the inflammatory pattern together with topography and tissue necrosis.

# Perivascular inflammation: A native schematic

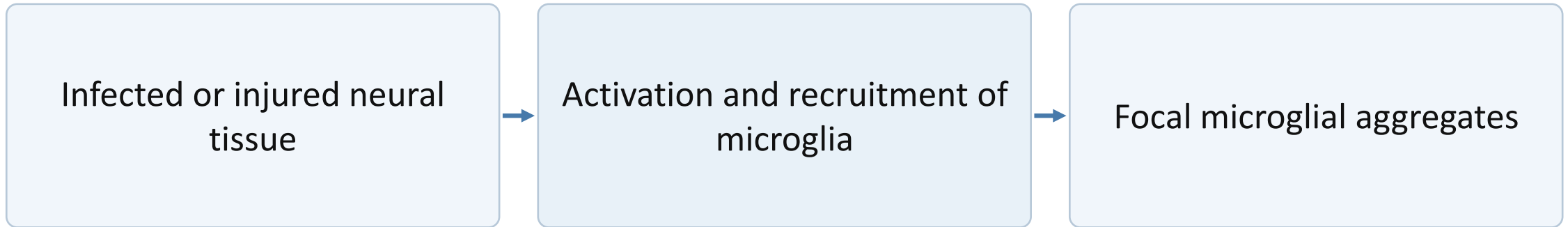


Schematic only; Not an H&E photomicrograph.

## Neuronophagia marks loss of injured neurons

- Neuronophagia is the phagocytic removal of damaged or dead neuronal debris.
- This feature in viral meningoencephalitis patterns.
- It is a morphologic consequence of neuronal injury, not a virus-specific inclusion.
- The extent of neuronal destruction helps explain persistent neurologic deficits.

## Microglial nodules arise during parenchymal injury



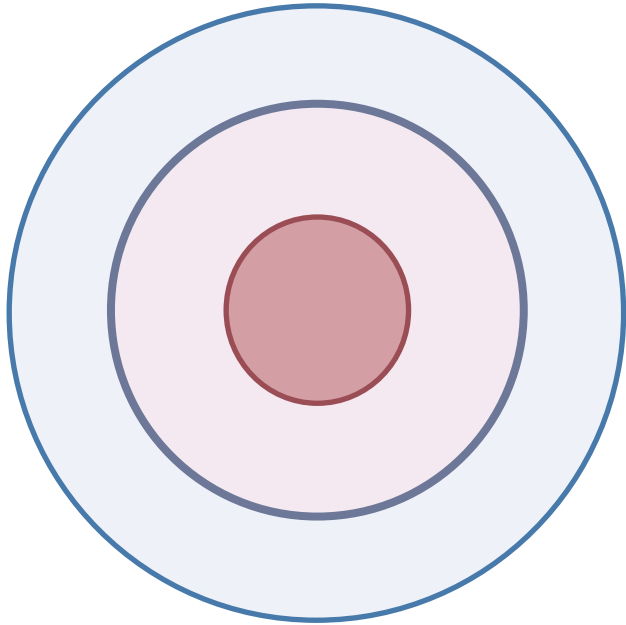
Microglial nodules characterize viral encephalitic inflammation, but are not HSV-specific.

## Cowdry type A inclusions: The viral cytopathic clue

- Intranuclear inclusions can be seen in HSV-infected neurons and glia.
- Cowdry type A inclusions have eosinophilic material with peripheral chromatin margination.
- They indicate herpesvirus-type nuclear cytopathic change but do not reliably distinguish HSV-1 from HSV-2.
- Their absence in a sample cannot rule out HSV encephalitis.

# Illustrated Cowdry type A nuclear change

*Native editable schematic; Not a specimen or a substitute for H&E confirmation*



## **Infected cell**

Large intranuclear inclusion

Peripheral chromatin displacement

May occur in neurons and glia

*HSV-1 and HSV-2 cannot be typed by inclusion morphology alone.*

## Syncytia provide another HSV cytopathic feature

- HSV can cause cell-to-cell fusion producing multinucleated syncytia.
- Viral inclusion-bearing multinucleated cells may be found in affected tissues.
- Syncytia are well illustrated in mucocutaneous HSV disease.
- They must not be presented as a substitute for evidence of brain involvement.

# How HSV histology is interpreted

## Pattern recognition

Necrosis and sometimes hemorrhage

Perivascular infiltrates

Intranuclear cytopathic change

## Etiologic confirmation

Immunohistochemical demonstration in tissue when obtained

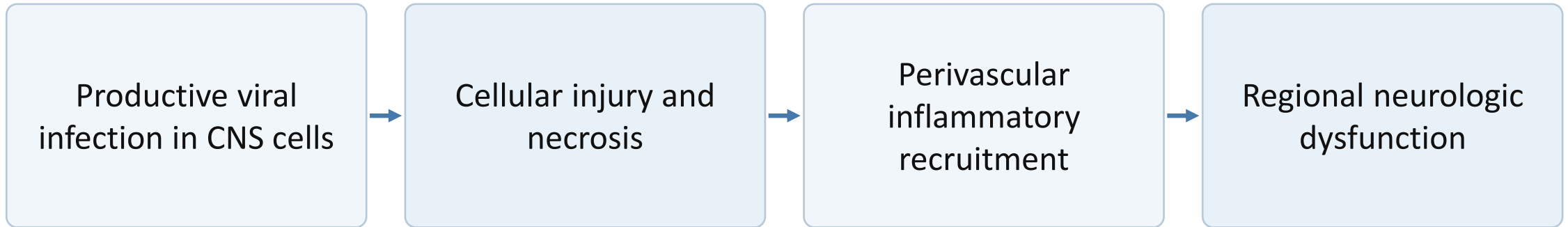
Molecular detection in the appropriate specimen

Clinical–radiologic–pathologic concordance

## Protracted cases may involve more diffuse regions

- Robbins explicitly contrasts classic focal distribution with slowly evolving encephalitis.
- Longer clinical evolution may be associated with more diffuse brain involvement.
- Atypical extent reduces the specificity of anatomic pattern alone.
- History, microbiology and pathologic data must be interpreted together.

# From molecular infection to observed brain pathology



In severe lesions, necrosis may be accompanied by hemorrhage.

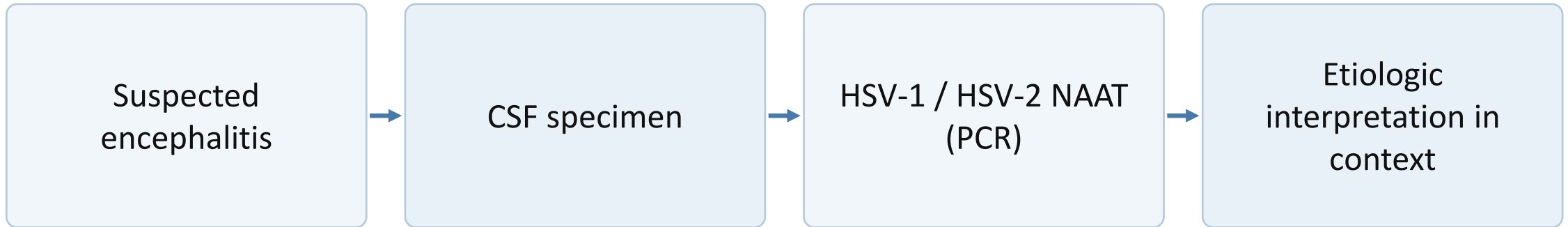
## MRI supports diagnosis through anatomic localization

- MRI is preferred to CT when evaluating suspected encephalitis (IDSA guideline).
- Temporal-lobe localization strengthens suspicion for HSV encephalitis.
- Imaging identifies the affected territory but does not by itself identify viral species.
- Imaging should be interpreted together with clinical findings and CSF testing.

## CSF analysis is central to the initial evaluation

- Unless contraindicated, obtain CSF in the diagnostic evaluation of encephalitis.
- Routine CSF studies assess inflammatory pattern and competing diagnoses.
- A CSF nucleic acid amplification test can establish a viral etiology.
- CSF microbiology is a clinical diagnostic route; Tissue histology is not routinely required.

## CSF HSV molecular testing: Recommended diagnostic test

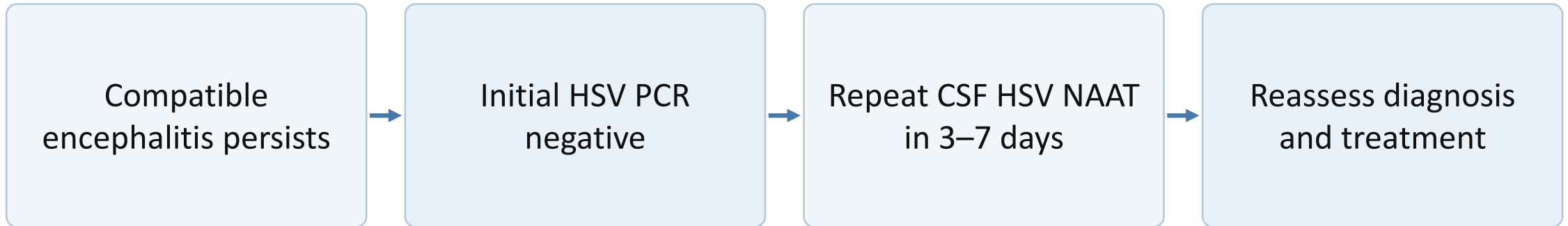


The 2024 IDSA/ASM laboratory guide recommends HSV-1/2 NAAT on CSF.

## CSF HSV NAAT is highly accurate but not infallible

- The 2024 IDSA/ASM guide reports CSF HSV NAAT sensitivity and specificity greater than 95%.
- An early false-negative result is possible despite a compatible clinical syndrome.
- A single negative test should not override highly suggestive clinical and temporal-lobe findings.
- The laboratory result must be interpreted against pretest probability.

## What to do when early CSF PCR is negative

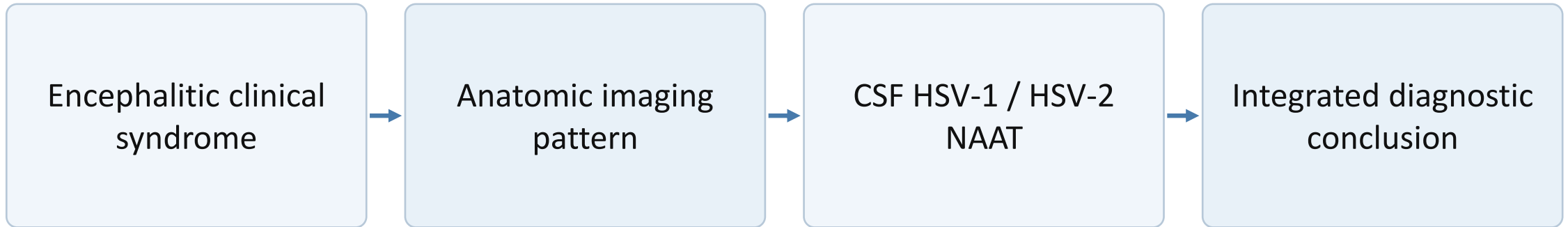


This repeat-testing recommendation is in the 2024 IDSA/ASM guide; Do not stop empiric therapy solely because of an early negative result.

## EEG addresses seizures rather than viral identity

- EEG may identify nonconvulsive seizures in an encephalopathic patient.
- Electrographic abnormalities generally do not establish the HSV etiology.
- Seizure detection changes supportive neurologic management.
- EEG complements but does not replace CSF virologic testing.

# Clinical evaluation integrates independent evidence



Treatable viral encephalitis requires rapid parallel evaluation and action.

## Empiric intravenous acyclovir should not wait for PCR

- The IDSA encephalitis guideline recommends prompt intravenous acyclovir for suspected encephalitis.
- Treatment should begin while diagnostic studies are pending when HSV is plausible.
- Delays increase the risk of death or severe neurologic sequelae.
- Treatment decisions require individual clinical assessment; This lecture is not a dosing protocol.

## Early antiviral therapy changes the natural history

- Substantial mortality reduction with antiviral treatment.
- The drug suppresses productive viral replication rather than reversing established necrotic tissue loss.
- Therefore rapid recognition matters even before complete etiologic confirmation.
- Persistent deficits can remain despite successful control of infection.

## Why brain biopsy is not the routine first test

- CSF molecular assays provide etiologic information without neurosurgical tissue sampling.
- The IDSA encephalitis guideline does not recommend routine brain biopsy.
- Biopsy may be considered in unexplained deterioration despite appropriate treatment.
- When tissue is obtained, morphology and targeted immunohistochemistry can be integrated.

## HSV-1 versus HSV-2 in central nervous system disease

| Feature              | HSV-1                               | HSV-2                                                 |
|----------------------|-------------------------------------|-------------------------------------------------------|
| Common CNS phenotype | Necrotizing encephalitis            | Adult meningitis; neonatal encephalitis               |
| Site clue            | Temporal/orbitofrontal predilection | No equivalent classic temporal predilection in source |
| Host context         | Multiple age groups                 | Neonates; HIV-associated severe disease               |
| Diagnosis            | CSF type-specific NAAT              | CSF type-specific NAAT                                |

*The viruses overlap; Patterns are tendencies, not absolute rules.*

## HSV-2: Important neonatal contrast

- HSV-2 acquisition in neonates during delivery from an actively infected genital tract.
- Severe neonatal encephalitis is a recognized consequence of infection.
- This differs from the classic HSV-1 temporal encephalitis teaching pattern.
- Type-specific CSF molecular testing distinguishes the viral types.

## Other neurotropic herpesviruses: Anatomic contrasts

| <b>Virus</b> | <b>Typical supplied Robbins context</b>      | <b>Distinctive tissue distribution</b>                  |
|--------------|----------------------------------------------|---------------------------------------------------------|
| HSV-1        | Sporadic encephalitis                        | Inferomedial temporal / orbitofrontal                   |
| VZV          | Latent sensory-neuron infection; zoster      | May cause CNS disease; not the classic HSV-1 lesion map |
| CMV          | Congenital or immunosuppressed CNS infection | Periventricular / subependymal regions                  |

## Arbovirus comparison: Shared histology, different context

- Many arboviral encephalitides cause lymphocytic cuffs, neuronophagia and microglial nodules.
- Those findings are not pathognomonic for HSV-1.
- Epidemiology and the distribution of CNS injury help prioritize etiologies.
- HSV-1 gains support from temporolimbic necrosis plus appropriate virologic results.

## Interpretation of candidate findings in suspected HSV-1

| Finding                  | What it supports                       | What it cannot prove                |
|--------------------------|----------------------------------------|-------------------------------------|
| Medial temporal injury   | Regional pattern compatible with HSV-1 | HSV-1 etiology in isolation         |
| Cowdry A inclusions      | Herpesvirus-type nuclear cytopathy     | HSV-1 rather than HSV-2             |
| Perivascular lymphocytes | Viral encephalitic inflammation        | Any single virus                    |
| Positive CSF HSV-1 NAAT  | HSV-1 nucleic acid in CSF              | Precise severity of tissue necrosis |

## Applied case: Acute limbic dysfunction

An adult develops rapidly evolving confusion, memory disturbance, and behavioral change. Brain MRI shows abnormalities in medial temporal regions.

**Which diagnosis should be prioritized and what test would establish the suspected viral etiology?**

Teaching interpretation · Prioritize HSV-1 encephalitis; Obtain CSF HSV-1/2 NAAT while promptly initiating clinically indicated empiric acyclovir.

## Applied case: A negative early HSV PCR

A patient has focal temporal MRI changes and encephalopathy. The initial CSF HSV PCR is negative early in the course.

**Does the initial negative result exclude HSV encephalitis?**

Teaching interpretation · No. With continued compatible suspicion, repeat CSF HSV NAAT in 3–7 days and continue clinical management rather than relying on one early result.

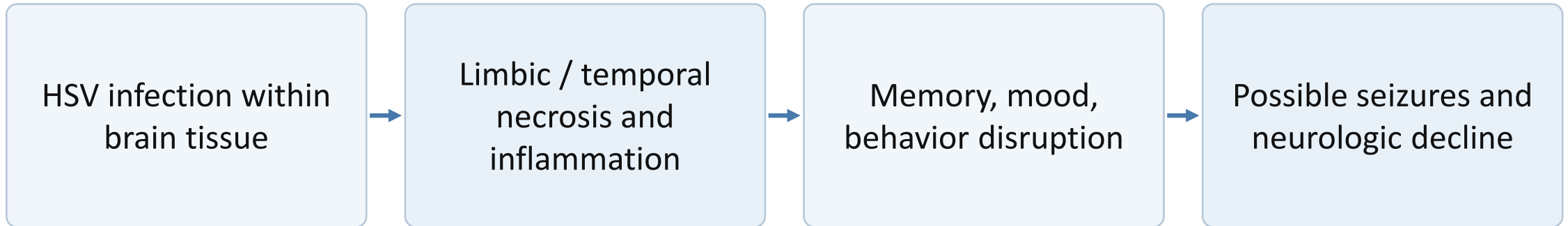
## Applied case: Pathology sign interpretation

A cerebral specimen shows necrosis, perivascular inflammatory cells, and occasional intranuclear eosinophilic inclusions.

**Which observations favor herpesvirus infection, and what limitation remains?**

Teaching interpretation · Cowdry-type nuclear cytopathic change supports herpesvirus infection; The pattern alone does not distinguish HSV-1 from HSV-2 and requires etiologic confirmation.

## A mechanistic chain explains the clinical presentation



The full pathology pattern links the underlying virus to focal clinical dysfunction.

## High-yield synthesis: Pathogen, site, pathology

- HSV-1 is an alpha-herpesvirus with epithelial replication and neuronal latency.
- The classic encephalitis pattern preferentially affects inferior/medial temporal and orbitofrontal regions.
- Parenchymal necrosis, often with hemorrhage, plus perivascular inflammation are key morphologic features.
- Cowdry type A inclusions may occur in neurons and glia.

## High-yield synthesis: Diagnostic and therapeutic action

- Suspect HSV encephalitis when progressive encephalopathy includes memory, behavioral change or seizures.
- Use MRI localization and CSF type-specific HSV NAAT to refine or confirm the working diagnosis.
- Repeat an early negative CSF HSV test when clinical suspicion persists.
- Initiate intravenous acyclovir promptly when HSV encephalitis is suspected; Do not await PCR.

# Selected references

## Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026). Chapter 28: The Central Nervous System (pp. 1150–1152); Chapter 8: Infectious Diseases (pp. 320–322).

## Clinical management (archived)

Tunkel AR, et al. Management of Encephalitis: IDSA Clinical Practice Guidelines. Clin Infect Dis. 2008;47:303–327. doi:10.1086/589747.

## Laboratory diagnosis (current 2024)

Miller JM, et al. IDSA/ASM Guide to Utilization of the Microbiology Laboratory, 2024. Clin Infect Dis. doi:10.1093/cid/ciae104.