

West Nile Virus

Pathogenesis, neuroinvasive disease, and neuropathology

An integrated clinicopathologic lecture

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Learning objectives

- Trace mosquito-borne transmission through skin, lymph nodes, and blood to the CNS.
- Distinguish febrile disease from neuroinvasive syndromes and their outcomes.
- Recognize characteristic neuropathologic reactions and diagnostic approaches.

Two clinical trajectories

Mild / self-limited

- Usually silent infection
- Symptomatic illness may be febrile
- Recovery without neuroinvasion

Neuroinvasive

- Meningitis, encephalitis, or both
- Potential spinal-cord involvement
- Long-term cognitive and neurologic effects

Clinical breadth is a defining feature of West Nile virus infection.

Etiologic identity

- West Nile virus is an arthropod-borne virus (arbovirus).
- It belongs to the flavivirus group.
- The pathogen causes an acute systemic viral infection; CNS disease develops in a minority.

Flavivirus context

Flavivirus group

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graph TD; A[Flavivirus group] --- B[ ]; B --- C[West Nile virus]; B --- D[Dengue viruses]; B --- E[Yellow fever virus];
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West Nile virus

Dengue viruses

Yellow fever virus

Shared viral grouping is not evidence of identical clinical syndromes.

Geographic distribution

- A broad geographic range.
- Regions named include Africa, the Middle East, Europe, Southeast Asia, and Australia.
- Geographic familiarity matters when interpreting a compatible febrile or neurologic syndrome.

United States: Emergence and spread

1999

**First detected in New
York City**

**Spread across the United
States**

Historical emergence; Not a current surveillance update.

Reported burden

- Approximately 1,000–3,000 U.S. Cases per year since 2013.
- This is a historical textbook characterization, not a live incidence estimate.
- Reported cases are distinct from all infections, because many infections are asymptomatic.

Reservoir and vector are distinct

Birds: Reservoir

- Infected birds develop prolonged viremia.
- Birds are the major reservoir for West Nile virus.

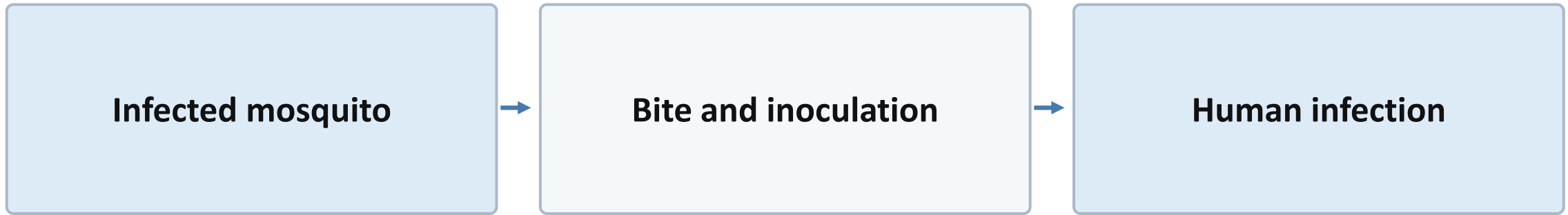
Mosquitoes: Vector

- Transmit virus to birds and mammals.
- A bite is the usual acquisition route in humans.

Humans are incidental hosts

- The mosquito–bird cycle maintains virus in nature.
- Humans become infected incidentally rather than serving as the major reservoir.
- Epidemiologic exposure is therefore informative without establishing disease.

Mosquito-borne acquisition



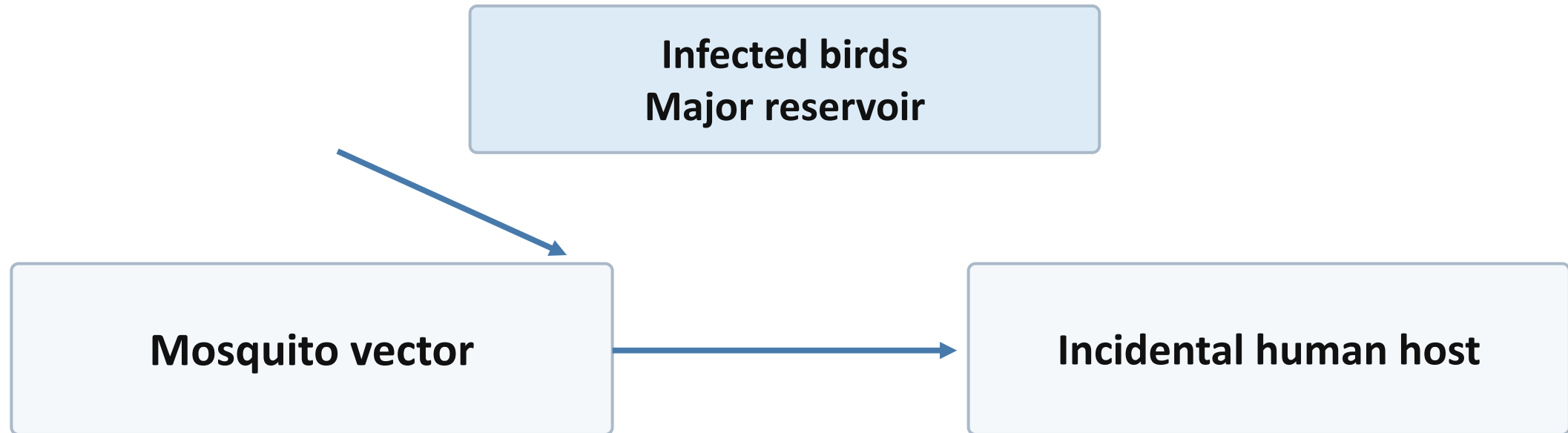
Most affected patients acquire West Nile virus through a mosquito bite.

Less common transmission routes

Route	Mechanism named by Robbins
Blood products	Transfusion
Donated organ	Transplantation
Maternal–child	Transplacental spread
Breastfeeding	Milk-associated transmission

These routes are less common than mosquito-borne acquisition.

Ecologic transmission schematic

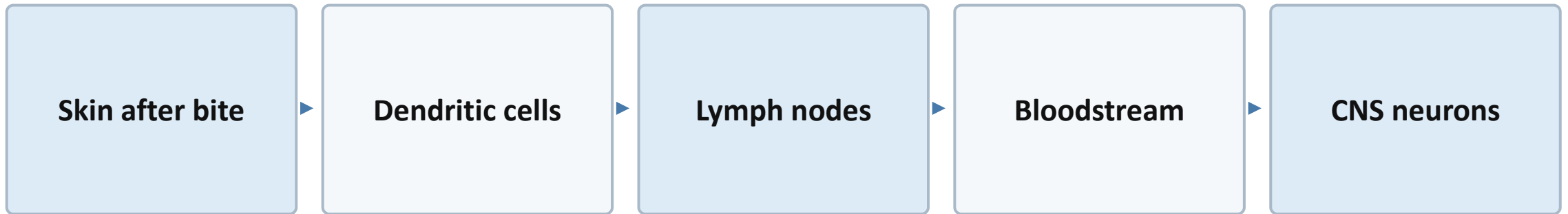


Bird–mosquito cycle maintains transmission; Human infection is incidental.

Transmission is not synonymous with severity

- Exposure route describes acquisition, not the resulting clinical phenotype.
- After infection, the spectrum extends from silent infection to meningoencephalitis.
- Host factors and neuroinvasion are relevant to severe outcomes.

Pathogenesis: Route from skin to neuron



The sequence follows the core mechanism, Chapter 8.

Initial site: Mosquito inoculation

Mosquito bite



Viral entry into skin



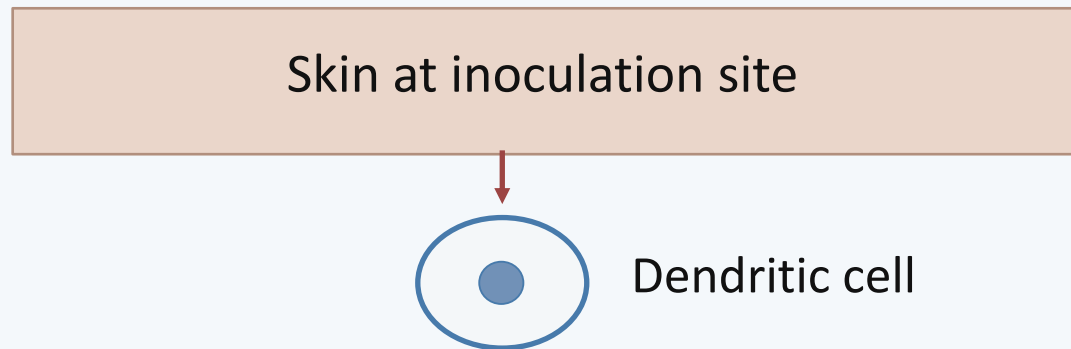
Local replication begins

Inoculation is the initiating event in the usual human infection route.

The skin is not merely an entry site: It is an early replication compartment.

Skin dendritic cells amplify infection

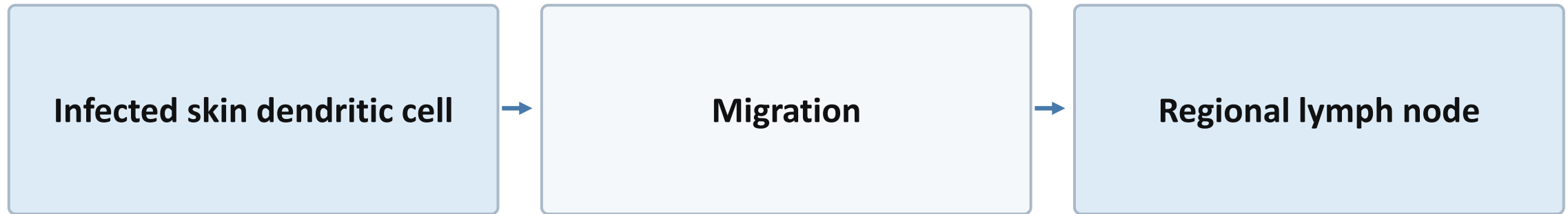
Virus replicates in skin dendritic cells.



Clinical / pathologic meaning

- Dendritic cells participate in an early stage of infection.
- Their subsequent migration links local infection to regional lymphoid tissue.

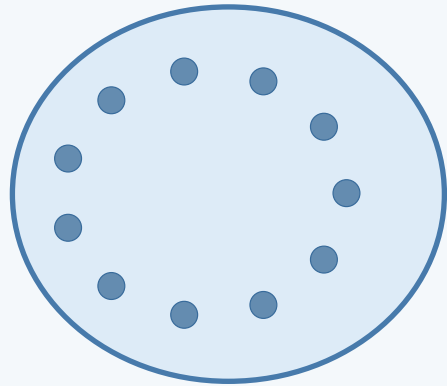
Migration to draining lymph nodes



The pathogen exploits cell trafficking to reach a new replication compartment.

Lymph nodes provide additional replication

West Nile virus replicates further within lymph nodes.

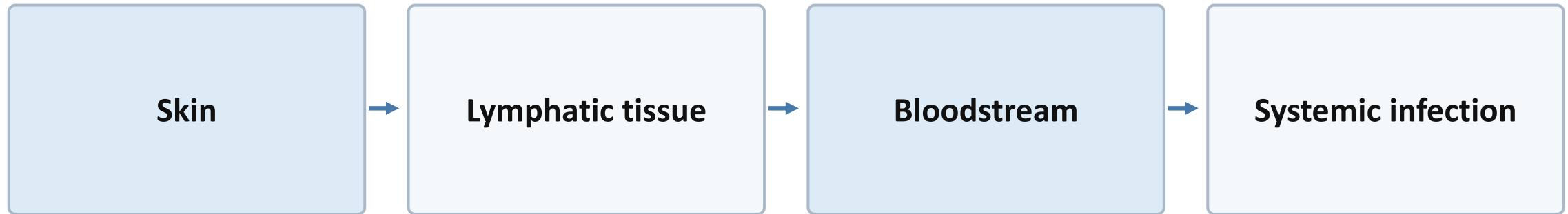


Lymph node

Clinical / pathologic meaning

- Lymph-node replication occurs after movement from the inoculation site.
- This precedes entry of virus into the circulation.

Viremia connects local and systemic disease



Viremia is a mechanistic bridge between local replication and dissemination.

Crossing the blood–brain barrier

In some infected persons, virus crosses the blood–brain barrier.

Blood



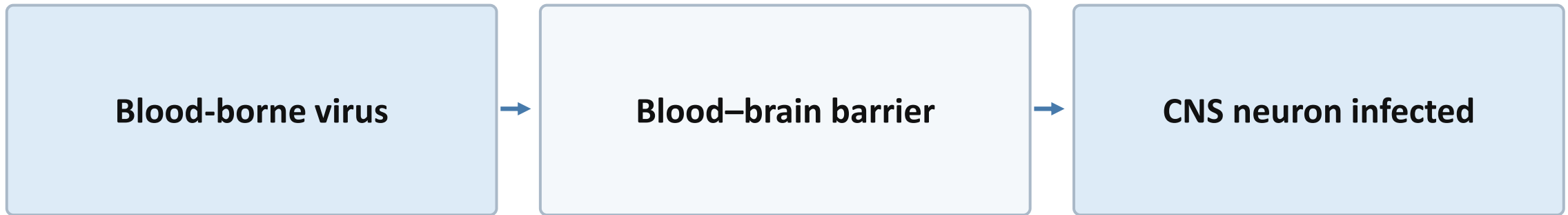
CNS compartment

Viral entry

Clinical / pathologic meaning

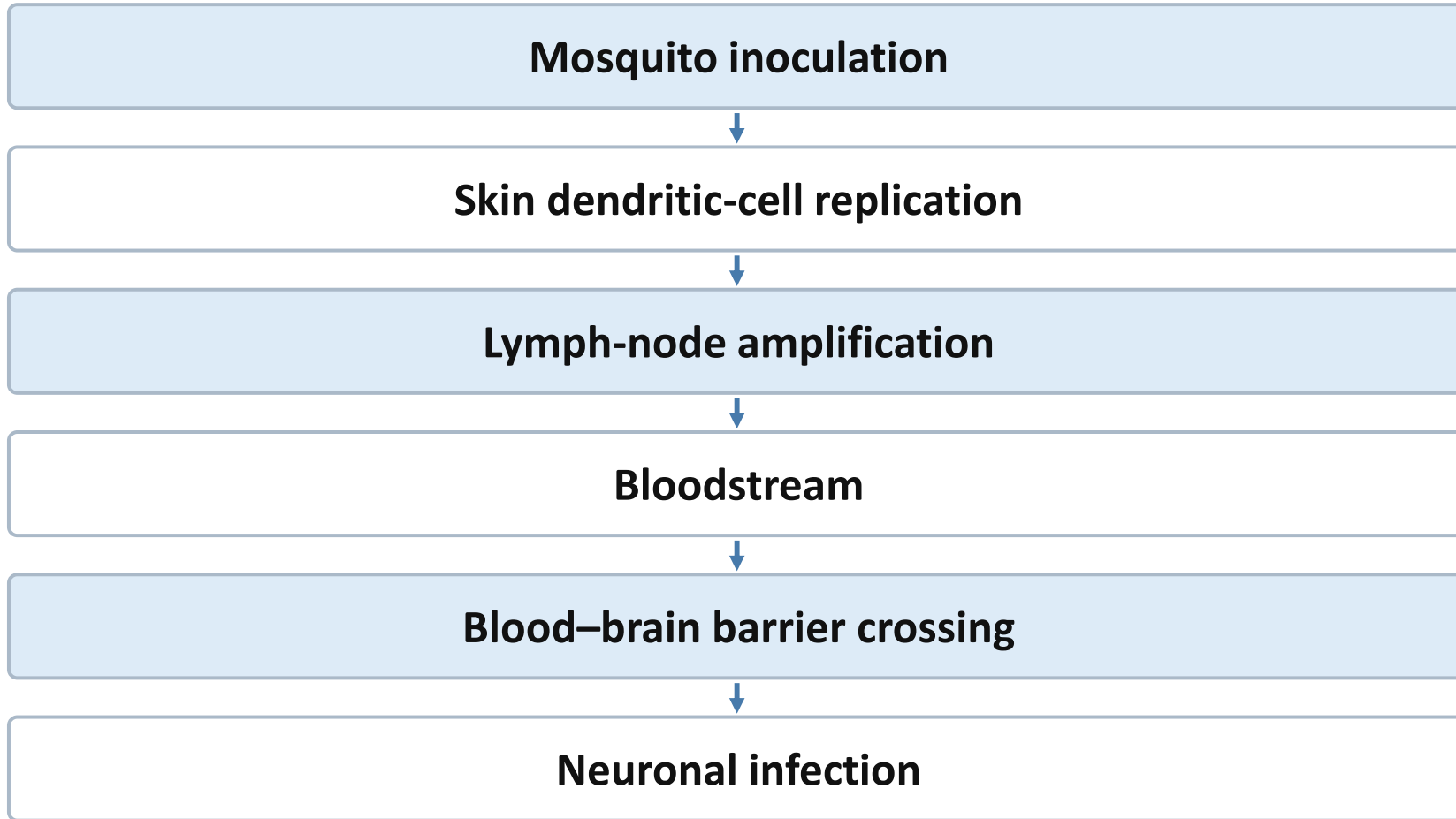
- Neuroinvasion occurs after systemic dissemination.
- This distinguishes ordinary systemic infection from direct CNS infection.

Neuronal infection defines neuroinvasion



The textbook specifically identifies neurons as infected CNS cells.

Pathogenesis: The integrated sequence



Pathogenic sequence; Neuroinvasion occurs only in some infected persons.

Neuroinvasion is uncommon

Most

Infections asymptomatic

~20%

Symptomatic febrile illness

~1 in 150

CNS complications

The three categories are not equivalent denominators; Do not add the proportions.

Host and disease course are not identical

Infection events

- Mosquito acquisition
- Early tissue replication
- Viremia

Clinical outcomes

- Asymptomatic infection
- Febrile systemic illness
- Rare neuroinvasive disease

Asymptomatic infection predominates

- Most infections do not produce a recognized clinical syndrome.
- Absence of symptoms does not negate infection.
- Symptom-based clinical series do not enumerate all infected individuals.

The acute febrile illness

- About 20% of infected persons develop symptoms.
- Fever and headache commonly frame the illness.
- Myalgia and fatigue add systemic symptoms without requiring CNS infection.

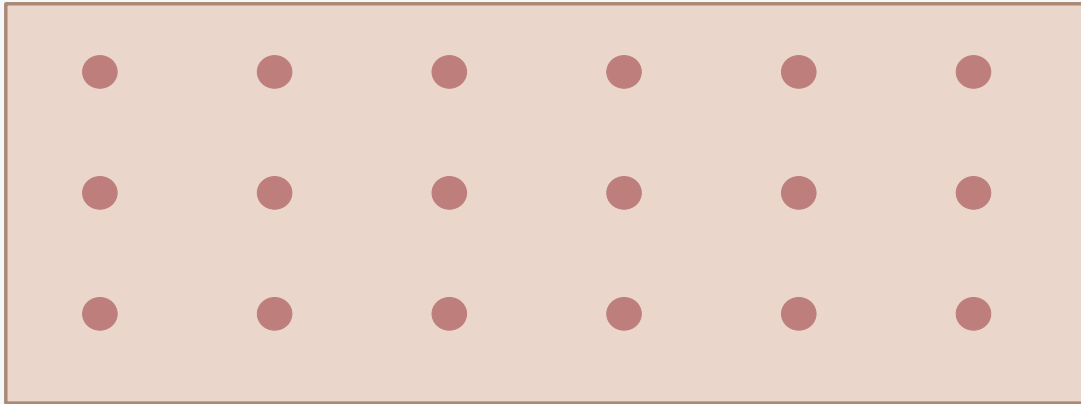
Systemic and gastrointestinal manifestations

Constitutional	Gastrointestinal
Fever	Anorexia
Headache	Vomiting
Myalgia / fatigue	Diarrhea

These symptoms are listed for symptomatic West Nile virus infection.

Maculopapular rash

A maculopapular rash occurs in approximately half of symptomatic cases.



Schematic: Maculopapular eruption

Clinical / pathologic meaning

- The denominator is symptomatic infections—not all infections.
- The rash is a clue within a compatible systemic illness, not a standalone etiologic diagnosis.

Interpreting the febrile phenotype

- Constitutional, gastrointestinal, and cutaneous features may coexist.
- These symptoms do not, by themselves, establish neuroinvasive disease.
- Progression to meningeal or cerebral dysfunction changes the clinical category.

Forms of neuroinvasive disease

CNS complications

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graph TD; A[CNS complications] --- B[Meningitis]; A --- C[Encephalitis]; A --- D[Meningoencephalitis]
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Meningitis

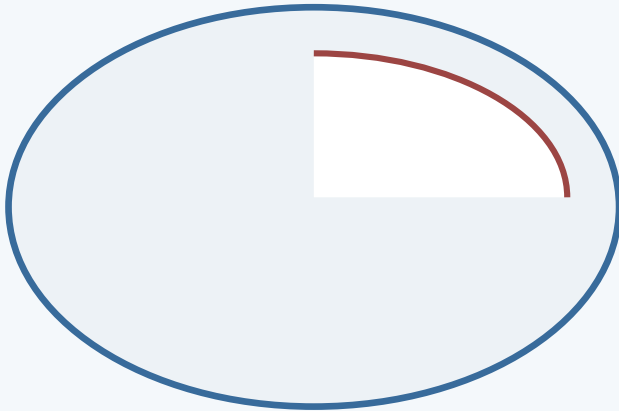
Encephalitis

Meningoencephalitis

These categories are explicitly listed.

Meningitis: Meningeal compartment

Meningitis primarily denotes inflammation of the leptomeninges and CSF space.



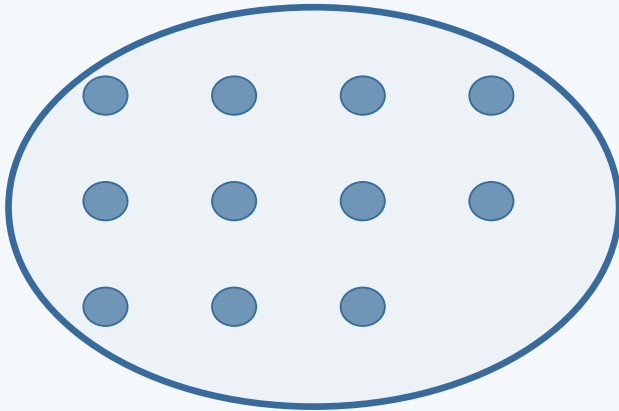
Leptomeningeal boundary (schematic)

Clinical / pathologic meaning

- West Nile virus can present with CNS meningitis.
- A meningeal syndrome is not equivalent to parenchymal encephalitis.

Encephalitis: Brain parenchyma

Viral encephalitis denotes infection and inflammation of brain parenchyma.



Parenchymal involvement (schematic)

Clinical / pathologic meaning

- Confusion, delirium, seizures, or reduced consciousness may indicate encephalitic involvement.
- Meningeal inflammation commonly accompanies viral encephalitis.

Meningoencephalitis: Two compartments

Meningeal component

- Leptomeningeal inflammation
- CSF inflammatory response

Parenchymal component

- Neuronal injury
- Microglial response and focal necrosis

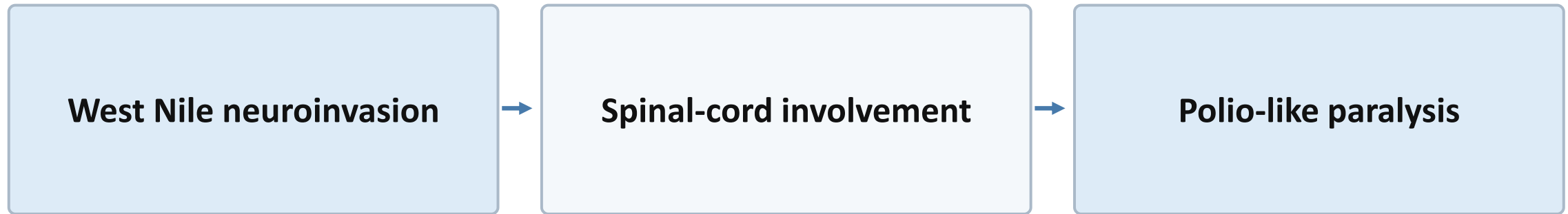
Combined disease has consequences beyond isolated meningeal irritation.

Neurologic deficits in arboviral encephalitis

Generalized	Focal
Confusion / delirium	Reflex asymmetry
Seizures	Ocular palsies
Stupor or coma	Localizing neurologic abnormalities

Chapter 28 describes these across arthropod-borne viral encephalitides; Not all findings occur in every WNV patient.

Spinal-cord involvement produces paralysis



The Chapter 28 CNS discussion explicitly links WNV spinal-cord involvement to a polio-like syndrome.

CNS disease spans several compartments

Leptomeninges

Brain parenchyma

Spinal cord

Meningitis, encephalitis, and WNV-related spinal disease are distinct but potentially overlapping sites.

Who is at greater risk of severe disease?

- Older adults are at greater risk.
- Immunosuppressed individuals are also at greater risk.
- These risk associations concern severe disease, not exclusive susceptibility to infection.

Uncommon extracerebral complications

Organ	Rare complication named
Liver	Hepatitis
Heart	Myocarditis
Pancreas	Pancreatitis

Do not overstate the frequency of these complications.

Meningoencephalitis can be fatal

~10%

Mortality among meningoencephalitis cases

~1 in 150

CNS disease among all infections

The 10% estimate and 1-in-150 frequency use different denominators.

Long-term neurologic consequences

- Many survivors of meningoencephalitis have persistent sequelae.
- Cognitive impairment is specifically described.
- Other neurologic impairment can persist after the acute phase.

Clinical probability: Mind the denominator

Textbook statement	Population being counted
20% symptomatic	All infected persons
Rash in ~half	Symptomatic persons
CNS disease ~1 in 150	All infections
Meningoencephalitis mortality ~10%	Patients with meningoencephalitis

Do not combine these conditional probabilities as though they use the same denominator.

CSF profile in arboviral encephalitis

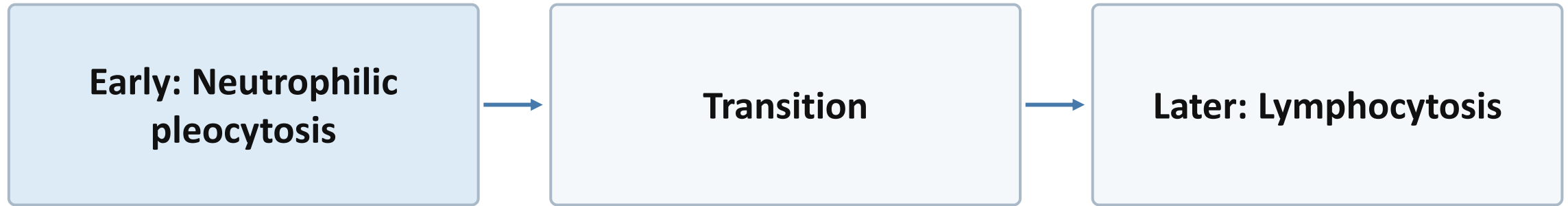
Appearance and pressure

- Usually colorless fluid
- Pressure may be slightly elevated

Chemistry and cells

- Protein elevated; Glucose normal
- Early neutrophils shift to lymphocytes

CSF cell pattern evolves with time



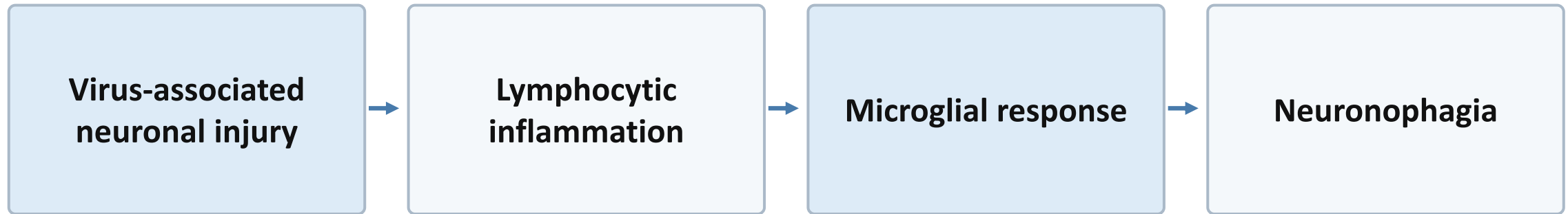
Time of lumbar puncture affects the cytologic impression in arboviral encephalitis.

Protein and glucose in arboviral CSF

Parameter	Typical textbook pattern
Protein	Elevated
Glucose	Normal
Pressure	Slightly elevated
Appearance	Usually colorless

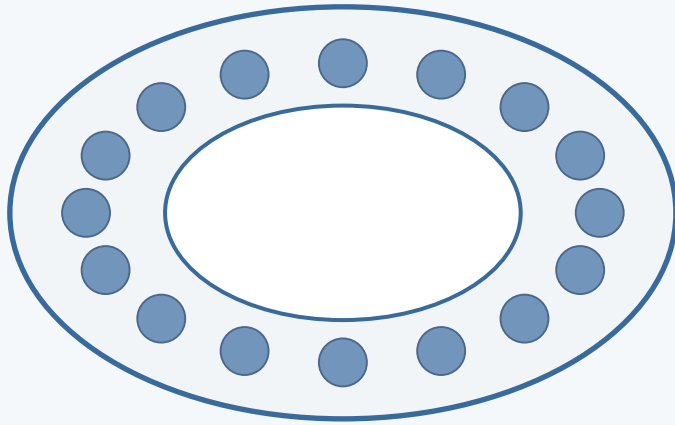
Pattern supports but does not uniquely identify an arboviral cause.

The characteristic tissue reaction



Summary of characteristic WNV and broader arboviral encephalitis morphology.

Perivascular inflammation



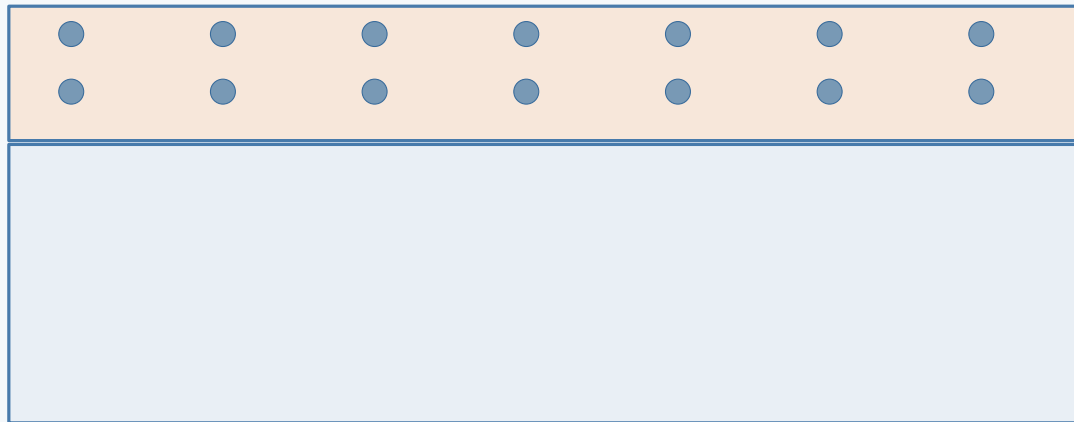
Lymphocytic perivascular cuff
Schematic — not a histologic specimen

Interpretation

- Lymphocytes accumulate around vessels in brain parenchyma.
- This is a characteristic pattern in arthropod-borne viral encephalitis.
- Distribution and severity vary among cases.

Leptomeningeal inflammation

Leptomeninges



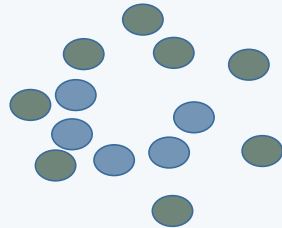
Adjacent CNS tissue

Schematic — not a histologic specimen

Interpretation

- West Nile autopsies show leptomeningeal chronic inflammation.
- Inflammation can coexist with a parenchymal viral encephalitis.
- Interpret with other sites and cell types in the CNS.

Microglial nodules



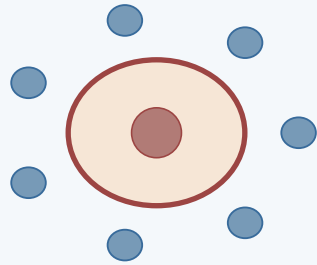
Focal aggregate of microglia

Schematic — not a histologic specimen

Interpretation

- Microglia form discrete cellular aggregates.
- These nodules are a stereotypic reaction to neuronal injury.
- Their presence alone does not prove which virus is responsible.

Neuronophagia



Injured neuron with adjacent phagocytes

Schematic — not a histologic specimen

Interpretation

- Injured or dead neurons are phagocytosed by microglial cells.
- The process signifies neuronal damage in the infected CNS.
- It may occur in gray and white matter foci of arboviral disease.

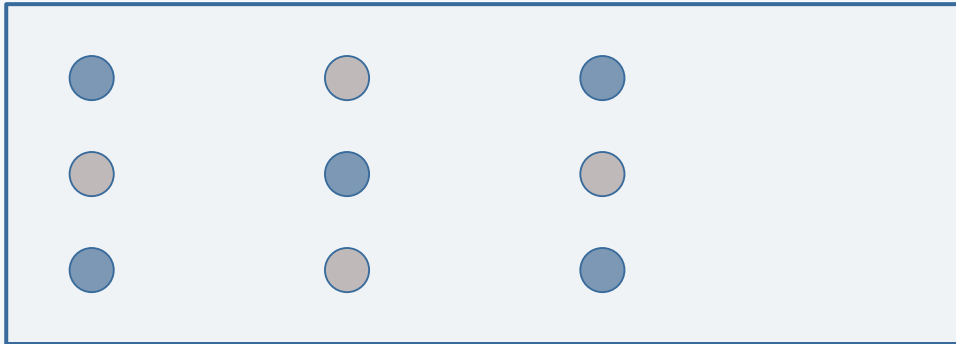
Anatomic distribution in fatal West Nile infection

Reported regions	Recorded changes
Temporal lobes	Inflammation, microglial nodules, neuronophagia
Brainstem	Inflammation, microglial nodules, neuronophagia

WNV-specific morphology from Chapter 8; Wording is “predominantly involving” these sites.

Arboviral encephalitis: Tissue necrosis

Multiple foci of necrosis may involve gray and white matter.



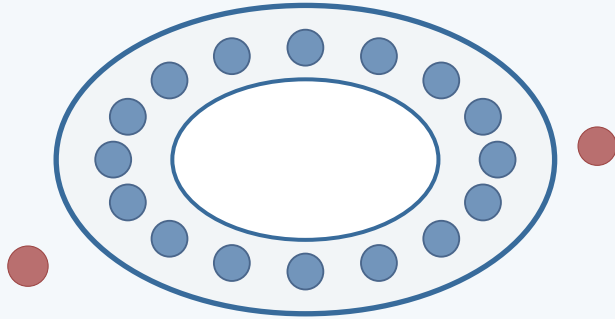
Schematic tissue injury foci

Clinical / pathologic meaning

- Single-neuron necrosis with neuronophagia is emphasized.
- Extent and severity vary across arboviral encephalitides.

Severe cases may show vascular injury

Necrotizing vasculitis with focal hemorrhage may occur in severe arboviral encephalitis.



Vessel injury with focal hemorrhage: Schematic

Clinical / pathologic meaning

- This is described as a severe-pattern feature.
- It is not a required finding for West Nile virus diagnosis.

Neuropathology and spinal signs

Anatomic substrate

- West Nile may involve the spinal cord.
- CNS infection can injure neuronal structures.

Clinical correlate

- A polio-like paralytic syndrome may follow.
- Do not equate all paralysis with poliovirus infection.

Why morphology does not identify the virus

What histology shows

- Perivascular lymphocytes
- Microglial nodules
- Neuronophagia / tissue necrosis

What it cannot establish alone

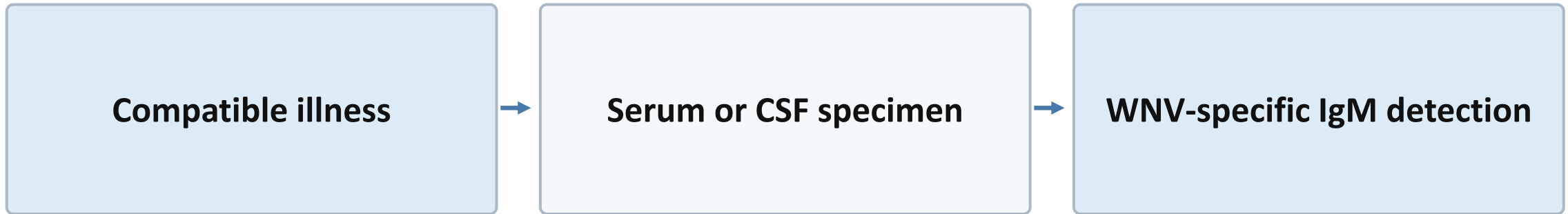
- Unique etiologic identity
- Specific arbovirus classification
- Virologic confirmation

When tissue is examined

Method named	Diagnostic role
Immunohistochemistry	Detection/identification of viral antigens
Molecular methods	Identification of viral nucleic acid
Ultrastructural methods	Viral characterization in tissue

Chapter 28 lists a combination of methods for tissue identification; Their performance varies by context.

Serologic diagnosis: Virus-specific IgM



Robbins Chapter 8 identifies virus-specific IgM in serum or CSF as the usual diagnostic approach.

Serum and CSF are different specimens

Serum IgM

- Supports recent virus-specific immune response.
- Must be interpreted with the illness and exposure context.

CSF IgM

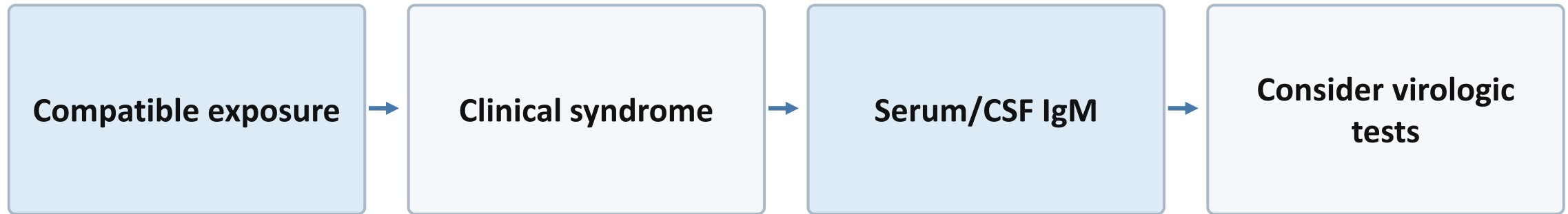
- Used when neuroinvasive infection is suspected.
- Interpret in the context of neurologic signs and CSF findings.

Alternative virologic methods

Method	What the test seeks
PCR-based assay	Viral nucleic acid
Viral culture	Recoverable virus

Both are named as additional diagnostic modalities by Robbins; The source does not provide sensitivity estimates.

Integrate history, syndrome, and laboratory



Illustrative diagnostic framework, not an externally validated clinical guideline.

West Nile and other arboviruses

Shared pattern	West Nile-specific clue from source
Mosquito/arthropod vector	Bird reservoir; Humans incidental
Meningoencephalitis	Risk of spinal-cord polio-like syndrome
Perivascular inflammation	Temporal-lobe/brainstem changes described at autopsy

No single listed feature is presented as pathognomonic.

West Nile versus HSV-1 encephalitis

West Nile

- Arthropod-borne, bird reservoir
- WNV can cause spinal paralysis
- Microglial nodules / neuronophagia

HSV-1

- Distinct viral etiology
- Classically necrotizing encephalitis
- Temporal-lobe involvement described

Case 1: Acute febrile illness

Illustrative case — not patient data

A patient develops fever, headache, myalgia, vomiting, and a maculopapular rash after probable mosquito exposure. No new neurologic deficits are described.

Which clinical category is most consistent, and what additional change would suggest neuroinvasion?

Case 1: Interpretation

- The described syndrome is compatible with symptomatic systemic infection.
- Rash is supportive context, not an etiologic proof.
- Meningeal symptoms or altered cerebral function would shift concern toward CNS disease.

Case 2: Acute altered consciousness

Illustrative case — not patient data

An older adult with a compatible febrile illness develops confusion and seizures. Cerebrospinal fluid shows elevated protein with normal glucose.

What syndrome is suggested, and which laboratory approach does Robbins emphasize?

Case 2: Interpretation

- Parenchymal neurologic dysfunction raises concern for encephalitis or meningoencephalitis.
- Age increases concern for severe West Nile virus disease.
- WNV-specific IgM in serum or CSF is the usual diagnostic method described.

Case 3: Acute paralysis

Illustrative case — not patient data

A patient with suspected arboviral encephalitis develops limb paralysis. The syndrome resembles poliomyelitis clinically.

What anatomic extension of West Nile infection can account for this presentation?

Case 3: Interpretation

- Spinal-cord involvement in West Nile encephalitis can produce polio-like paralysis.
- The syndrome is a clinicopathologic correlate of neuroinvasive infection.
- Clinical similarity to poliomyelitis does not establish poliovirus etiology.

Integrated clinicopathologic conclusions

- Reservoir birds and mosquito vectors explain usual acquisition.
- Skin → lymph nodes → blood → CNS provides the pathogenic sequence.
- Neuroinvasive disease is uncommon but may cause death or lasting neurologic injury.
- Lymphocytic inflammation, microglial nodules, and neuronophagia support an encephalitic process.

Textbook sources

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 8, “West Nile Virus,” p. 318.

Same textbook, Chapter 28, “Viral Meningoencephalitis” and “Arthropod-Borne Viral Encephalitis,” pp. 1150–1151.