

Neuroborreliosis

(Lyme disease)

Pathogenesis, neuropathology and clinicopathologic reasoning

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Learning objectives

Recognize

Define neuroborreliosis and its clinical phenotypes.

Explain

Connect spirochetal persistence, immune activation and pathology.

Interpret

Distinguish CSF abnormalities from rare autopsy findings.

Integrate

Locate nervous-system disease within the phases of Lyme infection.

What is neuroborreliosis?

Nervous-system involvement by Borrelia-associated Lyme disease.

Part of a multisystem arthropod-borne spirochetal infection.

Clinical expression ranges from meningeal to cranial-nerve, peripheral-nerve and encephalopathic syndromes.

INTERPRETATION

The label identifies the involved organ system, not one uniform neurological syndrome.

Its place among chronic bacterial CNS infections

Shared context

Chronic infection may involve meninges and brain.

Chronic bacterial CNS infections include *Borrelia*, tuberculosis and syphilis.

Distinct Lyme emphasis

Aseptic meningitis with cranial-nerve involvement.

Facial palsy, other polyneuropathies, encephalopathy.

The causal organism is a spirochete

Borrelia burgdorferi as the cause of Lyme disease in the United States.

Borrelia are spirochetal bacteria, not viruses or protozoa.

The neurological syndrome represents one possible manifestation of systemic infection.

INTERPRETATION

Etiology matters because pathogen-specific adaptive responses and immune escape shape the course.

Borrelia species differ geographically

United States

B. Burgdorferi predominates account.

Europe and Asia

B. Afzelii and B. Garinii additionally cause Lyme disease.

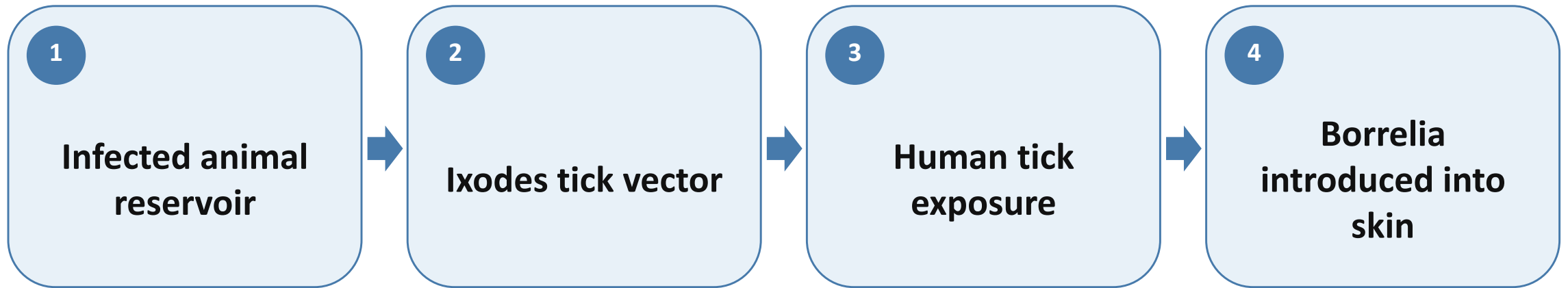
Shared transmission

Ixodes ticks transmit these agents.

Interpretation

Species distribution depends on region; Do not equate every exposure with one species.

Ixodes ticks transmit the infection



The vector links animal-host infection to human disease.

Reservoir ecology is species dependent

Rodent-associated cycle

Rodents are relevant reservoirs for Lyme Borrelia.

Ixodes ticks carry organisms to humans.

Bird-associated cycle

The textbook also identifies birds as reservoirs for B. Garinii.

Tick transmission remains the common route.

Endemic regions guide exposure assessment

Lyme disease occurs in the United States, Europe and Asia.

In the United States, the northeast and upper Midwest are emphasized.

Geographic context informs the plausibility of an Ixodes-associated illness.

INTERPRETATION

Exposure history is supporting context rather than a stand-alone proof of neuroborreliosis.

A tick may carry more than *Borrelia*

Borrelia

Spirochete associated with Lyme disease.

Ehrlichia

Potential Ixodes-associated coinfection in endemic settings.

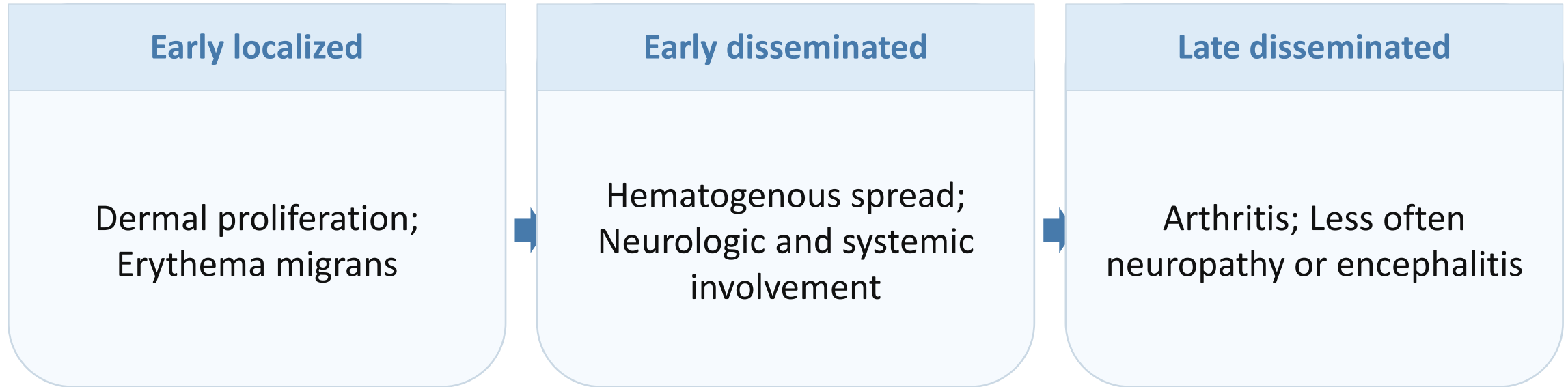
Babesia

Another organism that can be present in the same tick population.

Clinical principle

Do not attribute every symptom after a tick bite to a single pathogen.

Lyme disease follows a staged framework



Early localized infection begins in the dermis

Spirochetes multiply at the site of inoculation after the tick bite.

Their local spread produces an expanding erythematous skin lesion.

Fever or regional lymphadenopathy can accompany the rash.

INTERPRETATION

A cutaneous beginning helps explain how an eventual neurological illness can belong to a systemic infection.

Erythema migrans: The characteristic lesion

Distribution

An expanding area of erythema develops near inoculation.

Appearance

A pale center may be present; It is not required by the textbook description.

Course

The rash may resolve spontaneously over weeks.

Significance

Its presence connects a prior skin phase to later disseminated disease.

Skin pathology reflects inflammation

The Lyme-associated skin lesion shows edema.

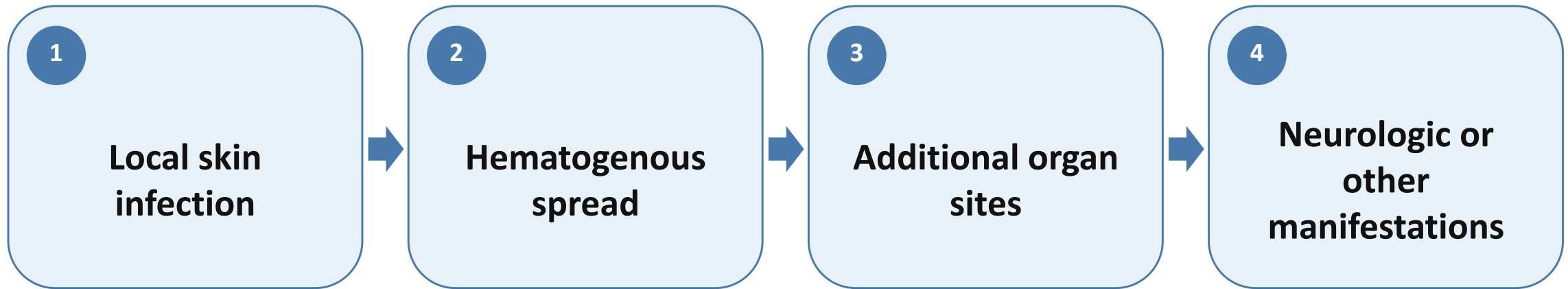
A lymphocytic–plasma cell infiltrate characterizes the reaction.

These observations are inflammatory findings, not unique histologic proof of *Borrelia*.

INTERPRETATION

The local immune response provides tissue-level context for later inflammatory organ injury.

Systemic dissemination changes the phenotype



Dissemination explains why rash, cardiac signs, joint symptoms and neurologic disease may coexist.

Early disseminated Lyme disease is multisystem

Skin / lymph nodes

Secondary skin lesions and lymphadenopathy.

Musculoskeletal

Migratory joint and muscle pain.

Cardiac

Arrhythmias can occur.

Nervous system

Meningitis, often with cranial-nerve involvement.

Four neurological phenotypes

Meningeal

Aseptic meningitis.

Cranial nerve

Facial nerve palsy and other cranial involvement.

Peripheral nerve

Other polyneuropathies.

Encephalic

Encephalopathy; Less commonly encephalitis.

Aseptic meningitis is a core presentation

Meningeal inflammation is explicitly included in the neuroborreliosis spectrum.

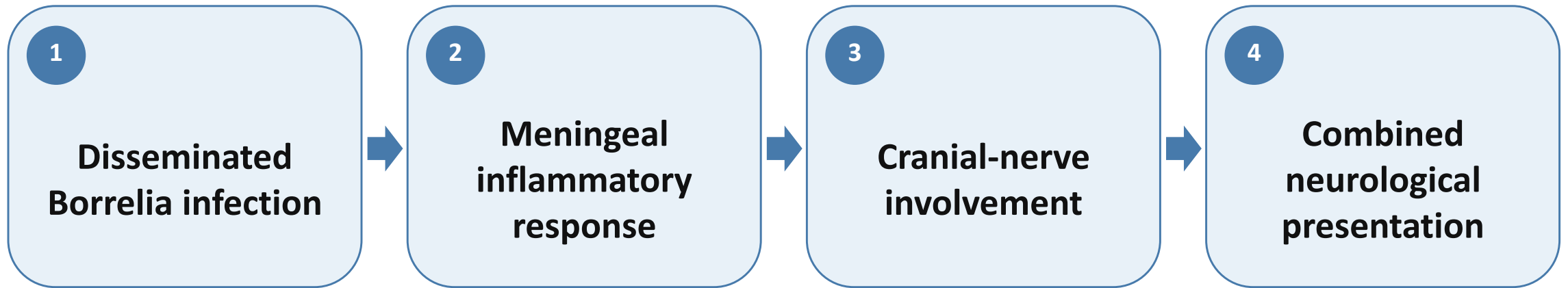
Robbins locates meningitis among early disseminated manifestations.

Cranial-nerve involvement may accompany the meningeal syndrome.

INTERPRETATION

A meningitis syndrome and cranial neuropathy can be two manifestations of the same infection.

Meningitis and cranial neuropathy can coexist



The source associates these features; The schematic does not assert a specific microscopic route.

Facial nerve palsy is a characteristic clue

Facial nerve palsy is specifically named in the neurological syndrome description.

It is one neurological phenotype, not a mandatory sign.

Its interpretation is strengthened by relevant Lyme exposure or other staged manifestations.

INTERPRETATION

A normal facial nerve examination cannot exclude other forms of neuroborreliosis.

The syndrome extends beyond the facial nerve

“other polyneuropathies” in the neurologic spectrum.

Late disseminated disease can less often involve polyneuropathy.

Peripheral nerve complaints therefore belong in the same differential framework as CNS features.

INTERPRETATION

Separate central and peripheral neurological involvement when describing the phenotype.

Encephalopathy is part of the spectrum

Encephalopathy is a recognized neurological manifestation.

Encephalitis is described in some late disseminated cases.

The two terms are not interchangeable: Avoid assuming all cognitive symptoms prove parenchymal infection.

INTERPRETATION

Use the clinical term supported by the evidence rather than equating all altered cognition with encephalitis.

Late neurological disease is less common

Late disseminated Lyme disease may occur months after inoculation.

Chronic large-joint arthritis is a dominant late manifestation.

Polyneuropathy or encephalitis occurs less often account.

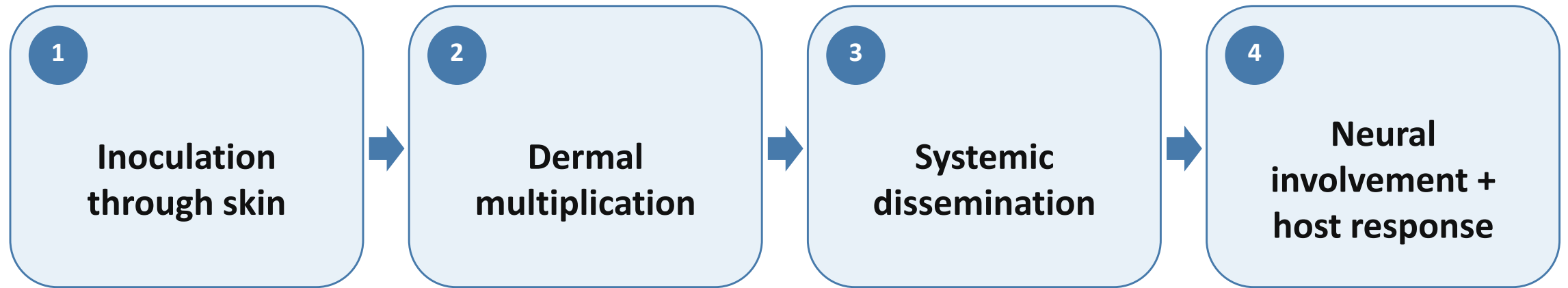
INTERPRETATION

Neurological timing should be interpreted alongside the full course of illness.

Clinical staging: Timing and phenotype

Stage	Characteristic involvement	Neurologic relevance
Early localized	Local skin / erythema migrans	Provides evidence of preceding infection
Early disseminated	Bloodborne multisystem spread	Meningitis and cranial nerves
Late disseminated	Arthritis and selected late effects	Less often neuropathy / encephalitis

A skin-to-nervous-system causal map



Conceptual sequence derived from the staged Lyme disease model.

Neurologic disease can accompany extra-CNS signs

Neurological observations

Aseptic meningitis

Facial palsy or other neuropathy

Encephalopathy

Concurrent systemic clues

Prior expanding rash

Migratory joint or muscle pain

Lymphadenopathy or cardiac
manifestations

Borrelia injury is not toxin driven

B. Burgdorferi does not produce the endotoxin or exotoxins invoked for many other bacterial injuries.

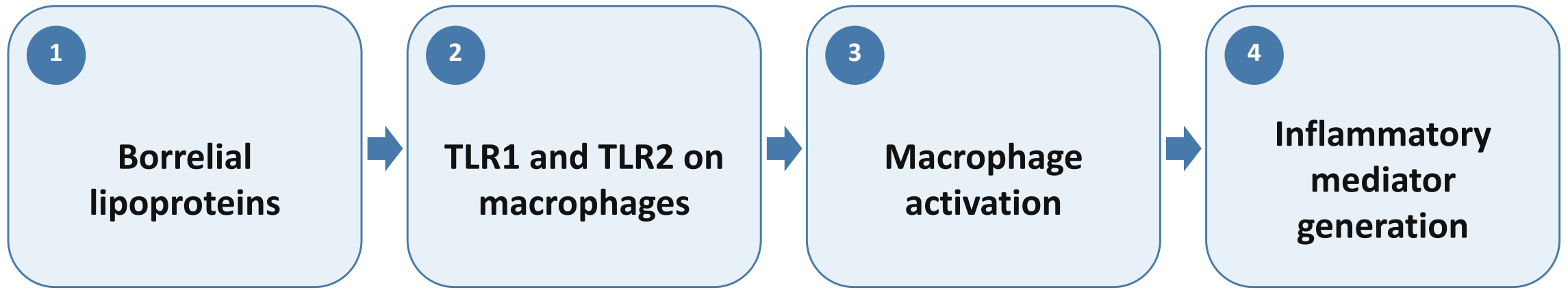
Much pathology is attributed to the host immune response.

Inflammatory tissue injury can persist despite attempts to clear infection.

INTERPRETATION

The host reaction is central to the pathogenesis model.

Innate immune recognition begins at TLR1/TLR2



Native recognition of bacterial lipoproteins initiates the innate immune response.

Macrophages release inflammatory cytokines

IL-6

One of the named proinflammatory mediators.

TNF

Another inflammatory cytokine released after receptor activation.

Reactive nitrogen

Bactericidal intermediates are generated.

Net effect

Microbial control and host inflammation occur together.

Microbicidal mechanisms are incomplete

Reactive nitrogen intermediates reduce the organism burden.

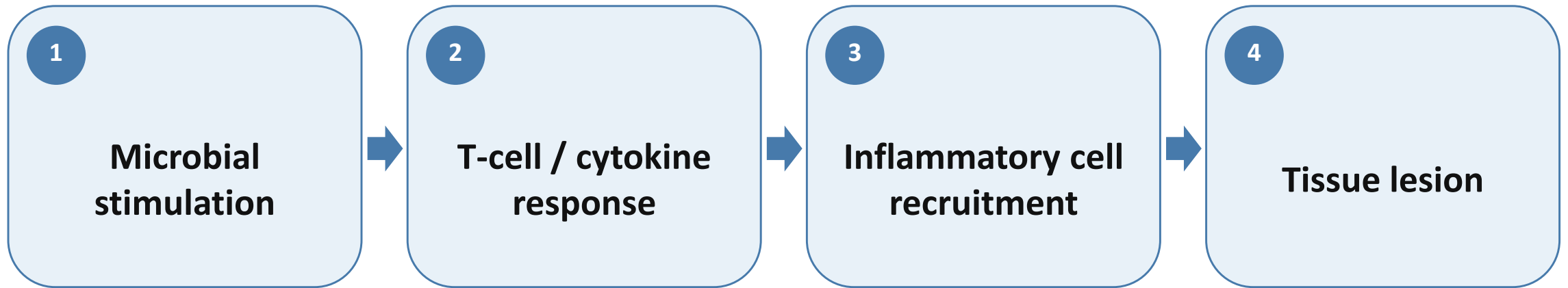
, this first response usually does not fully eliminate the infection.

A persisting organism can maintain antigenic stimulation and inflammatory responses.

INTERPRETATION

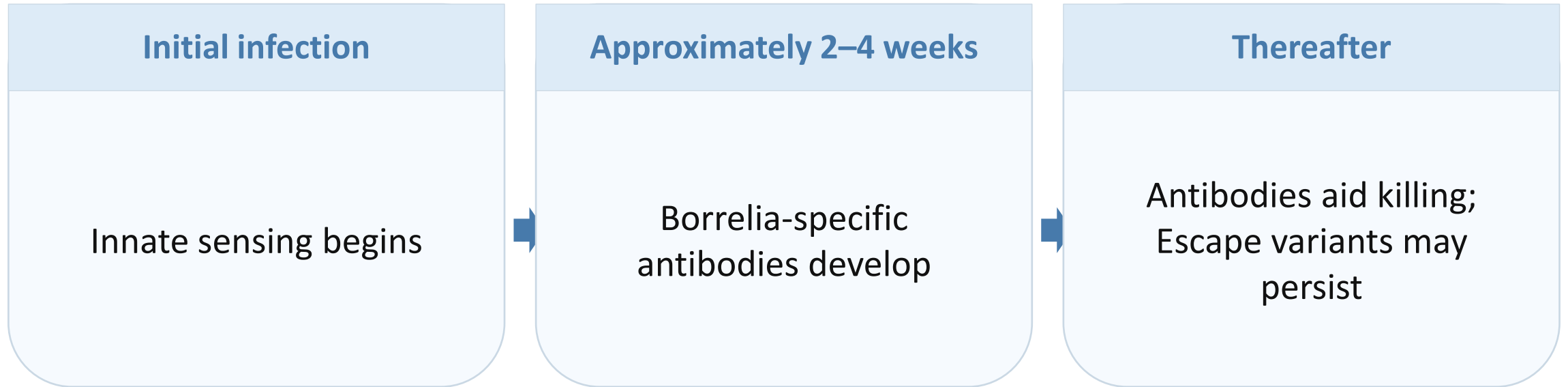
Partial clearance helps explain the transition from an acute encounter to prolonged disease.

T cells and cytokines sustain lesions

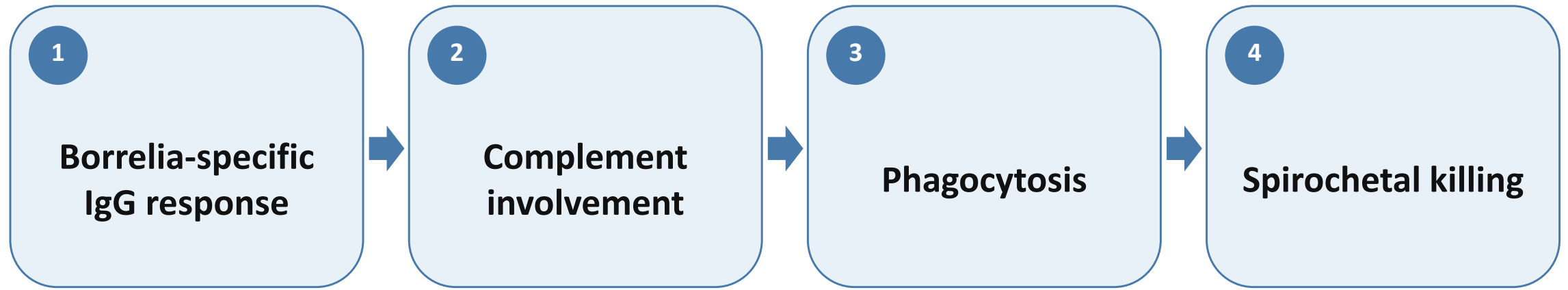


This is the proposed inflammation-centered mechanism; Not a claim of a unique CNS histologic sequence.

Humoral immunity develops after infection



Antibodies promote microbial clearance



Anti-Borrelia antibodies with complement-mediated microbial clearance.

Antibody emergence does not ensure eradication

Protective response

Antibodies recognize *Borrelia*.

Complement and phagocytosis kill organisms.

Evasion response

Bacterial surface proteins can change.

Variants escape established antibody recognition.

Outer surface protein C changes over time

Outer surface protein C (OspC) is needed during establishment of infection.

It is not required for persistence in the model presented.

Downregulation of OspC contributes to evasion of an evolving antibody response.

INTERPRETATION

Expression change can be as important as acquisition of new antigens.

VlsE antigenic variation supports persistence

A plasmid encoding a variable antigenic surface protein, VlsE.

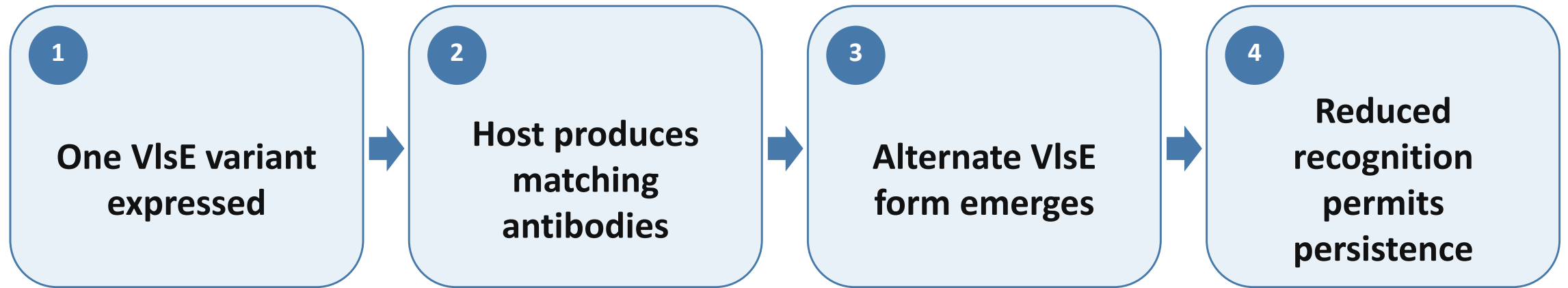
Alternative coding segments can be expressed next to a common promoter.

Antibodies against one expressed form select for organisms displaying another form.

INTERPRETATION

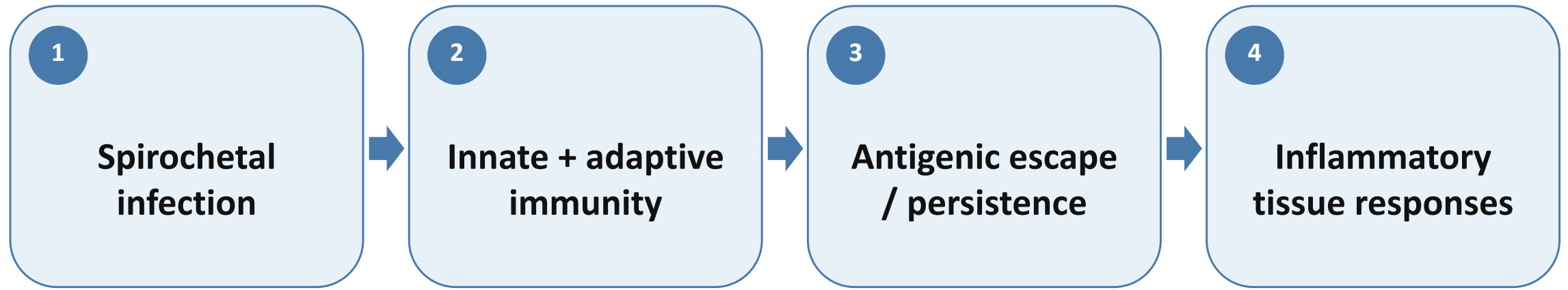
The mechanism creates moving targets for the host humoral immune response.

The VlsE immune-escape cycle



This is a simplified conceptual model of antigenic variation, not a measured evolutionary timeline.

An integrated pathogenesis model



Host defense and immune escape help account for prolonged or recurrent disease manifestations.

Meningitic CSF shows cellular inflammation

Lyme meningitis produces a hypercellular cerebrospinal fluid compartment.

This to a marked lymphoplasmacytic infiltrate.

The CSF finding reflects a host inflammatory response in the meningeal space.

INTERPRETATION

The key textbook CSF morphological feature is a lymphoplasmacytic response.

Antispirochete IgG can occur in CSF

The source describes antispirochete IgGs in Lyme meningitis CSF.

This supports the biological link between nervous-system inflammation and *Borrelia*-directed immunity.

The excerpt does not specify a validated CSF antibody-index threshold or sensitivity.

INTERPRETATION

Do not convert a qualitative textbook finding into a numerical diagnostic criterion.

CSF and brain parenchyma are different compartments

CSF in meningitis

Marked lymphoplasmacytic cellularity

Antispirochete IgGs

Rare autopsy brain findings

Focal microglial proliferation

Scattered extracellular organisms

Focal microglial proliferation at autopsy

Rare autopsied cases have shown focal microglial-cell proliferation in brain tissue.

Microglia are the resident immune-effector cell population in the CNS.

Robbins does not describe this finding as a pathognomonic lesion.

INTERPRETATION

Interpret the observed response as evidence of CNS inflammatory activation, not a specific diagnostic hallmark.

Scattered extracellular organisms at autopsy

Scattered extracellular organisms have been observed in rare autopsy material.

Their presence supplies direct morphologic evidence in those exceptional cases.

The source does not justify assuming that organisms will be visible in routine tissue sections.

INTERPRETATION

A documented rare observation must not be presented as a routinely demonstrable diagnostic sign.

Neuropathologic evidence has major limitations

Sampling

Only rare cases have undergone autopsy in the account.

Distribution

Microglial reaction is described as focal.

Detection

Organisms are scattered, not abundant.

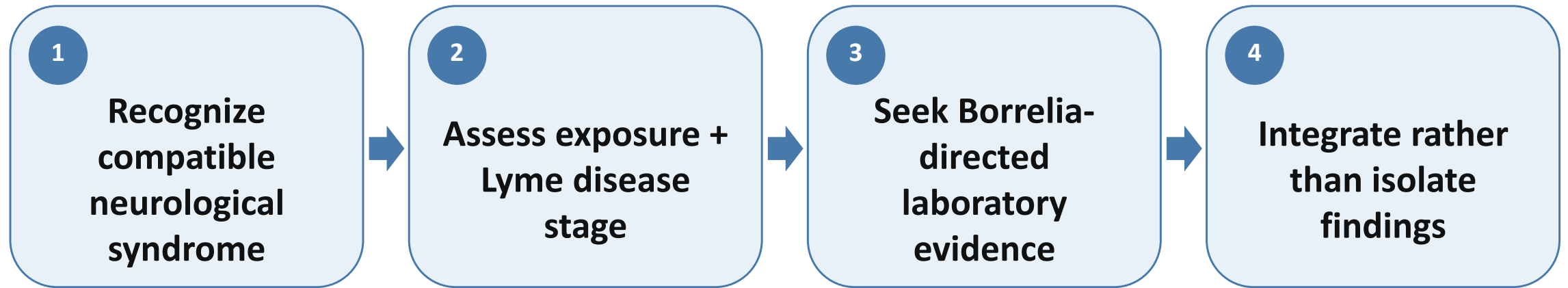
Inference

Neither distribution nor sensitivity can be quantified from this excerpt.

Morphology across affected compartments

Compartment	Textbook morphological feature	Interpretation
Dermis	Edema; lymphocytes and plasma cells	Inflammatory local lesion
CSF / meninges	Hypercellularity; lymphoplasmacytic infiltrate	Meningeal immune response
Brain at autopsy	Focal microglial proliferation	Parenchymal response in rare cases
Brain at autopsy	Scattered extracellular organisms	Occasional direct tissue evidence

Diagnosis is a clinicopathologic synthesis



The source provides principles rather than a complete modern neuroborreliosis case definition.

Serology is the principal Lyme diagnostic method

Serology as the main method of Lyme disease diagnosis.

The interpretation must relate a positive antibody response to the clinical syndrome.

The supplied excerpts do not supply a specific modern testing algorithm or assay thresholds.

INTERPRETATION

Do not confuse evidence of exposure or immune response with proof of the current site of disease.

PCR is discussed for infected tissues

PCR can be applied to infected tissue in Lyme disease.

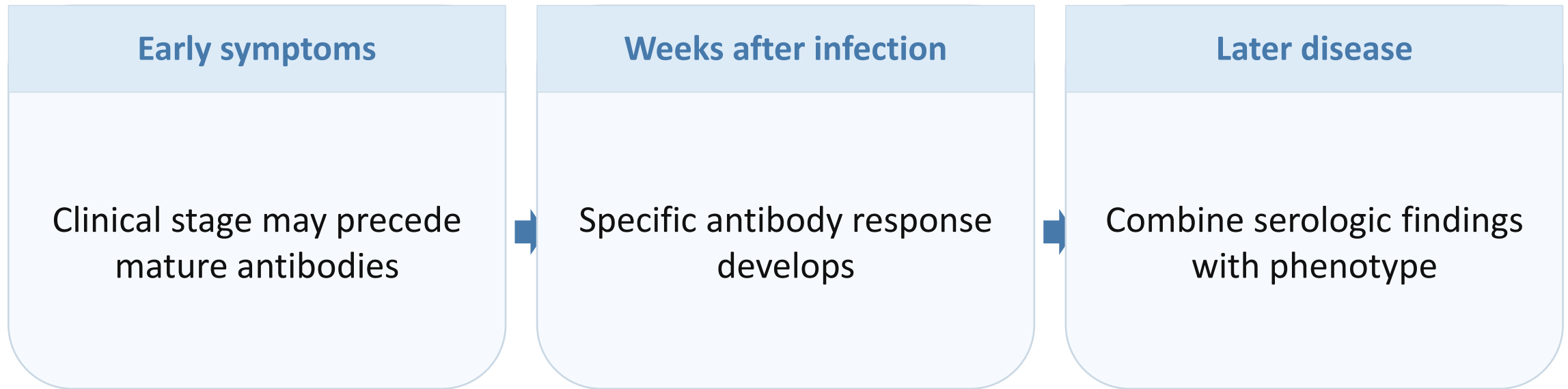
Synovial fluid is a specific application in Lyme arthritis.

Neither excerpt provides a validated CSF PCR rule-out strategy for neuroborreliosis.

INTERPRETATION

Specimen choice and diagnostic performance must not be extrapolated without supporting data.

Diagnostic timing must respect seroconversion



The source gives a 2–4-week antibody-development interval, not a complete testing schedule.

Meningitis differentials require syndromic care

Disease	Textbook emphasis	Important distinction
Neuroborreliosis	Aseptic meningitis; facial palsy	Borrelia-linked multisystem course
CNS tuberculosis	Chronic meningitis; basal complications	Different pathogen and pathologic pattern
Neurosyphilis	Meningovascular / paretic / tabetic disease	Different spirochete and syndrome spectrum

CNS versus peripheral nerve involvement

Central / meningeal

Aseptic meningitis

Encephalopathy

Encephalitis in some later cases

Cranial / peripheral

Facial-nerve palsy

Other cranial involvement

Polyneuropathies

Case 1: Cranial neuropathy after skin disease

Teaching scenario: A patient from an endemic area recalls an expanding erythematous lesion and later develops facial weakness.

Which Lyme stage and neurological phenotype best fit the sequence?

Early dissemination with cranial-nerve involvement is consistent with Robbins. The vignette is illustrative, not a patient record.

Case 2: Meningeal inflammation with IgG

Teaching scenario: A patient has an aseptic meningeal syndrome; CSF examination reveals lymphoplasmacytic cellularity and Borrelia-directed IgG.

What is the most defensible pathology interpretation?

These findings support a Borrelia-associated meningeal immune response. The excerpt alone does not establish a numerical definitive criterion.

Case 3: Delayed multisystem presentation

Teaching scenario: Months after a suspected tick exposure, a patient develops chronic large-joint inflammation and neuropathic symptoms.

What stage and cross-system connection should be considered?

A late disseminated pattern is plausible. Arthritis is prominent in this stage; Neuropathy is described less often.

Lyme arthritis illustrates systemic persistence

Large joints, particularly knees, are emphasized in Lyme arthritis.

Untreated late disease can produce prolonged joint attacks and erosion of cartilage.

This extraneural manifestation contextualizes neuroborreliosis within one systemic infection.

INTERPRETATION

Joint disease is relevant for staging and systemic integration, not evidence of CNS infection by itself.

Synovial pathology parallels immune activation

Synoviocyte hyperplasia and fibrin deposition occur.

Mononuclear inflammatory cells, including T cells, infiltrate the synovium.

Arteriolar onion-skin–like thickening and obliterative endarteritis may occur.

INTERPRETATION

The characteristic inflammatory joint response differs in tissue distribution from meningeal or cerebral findings.

Treatment context from the Robbins excerpt

Antibiotics active against *Borrelia* are effective for Lyme disease in the described clinical context.

Most Lyme arthritis cases are described as responding to antibiotic therapy.

The excerpts do not specify neuroborreliosis antibiotic selection, dose or treatment duration.

INTERPRETATION

A pathology lecture should not infer a therapeutic regimen from source text that does not provide one.

Frequent interpretive errors

Overgeneralization

Not every neuroborreliosis case has facial palsy.

Compartment error

CSF lymphoplasmacytosis is not identical to a brain biopsy pattern.

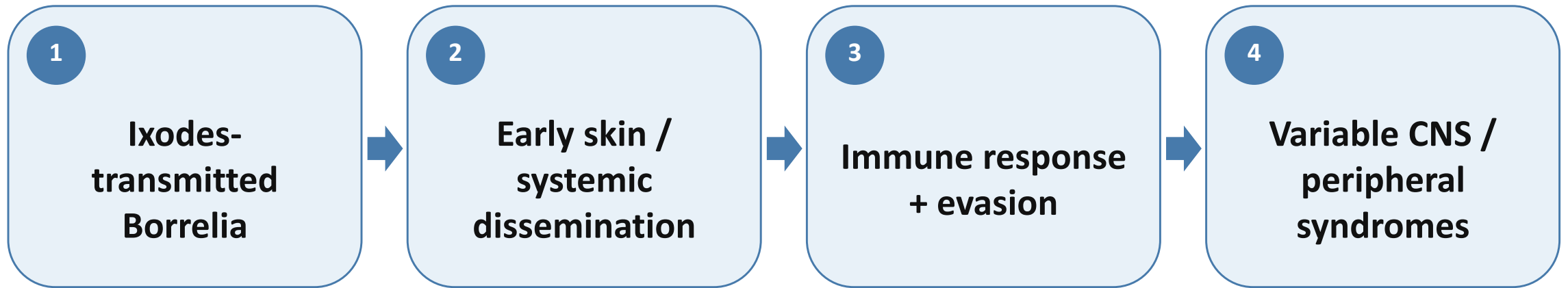
Diagnostic inflation

Qualitative CSF IgG is not a published threshold in these excerpts.

Morphology inflation

Rare autopsy observations are not routine diagnostic criteria.

Synthesis: Organism, host and neurological injury



Interpret neuroborreliosis as the neurological face of a host–pathogen interaction across disease stages.

The five defensible teaching conclusions

Organism

An Ixodes-borne *Borrelia* spirochete causes Lyme disease.

Mechanism

Innate inflammation, antibodies and antigenic variation shape persistence.

Context

Stage, exposure and systemic features anchor interpretation.

Neurology

Meningitis, cranial palsy, neuropathy and encephalopathy define the spectrum.

Pathology

CSF lymphoplasmacytosis contrasts with rare focal microglial brain findings.

Caution

Avoid unverified numerical diagnostic or therapeutic rules.

Source references

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).

The Central Nervous System — Neuroborreliosis (Lyme Disease).

Same textbook.

Infectious Diseases — Lyme Disease.

Same textbook.

Bones, Joints, and Soft Tissue Tumors — Lyme Arthritis.