

Lyme Disease

Etiology • immune pathogenesis • morphology • clinicopathologic correlation



A systemic Borrelia infection transmitted by Ixodes ticks

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Learning objectives

- Identify the *Borrelia* species, Ixodes vector, and reservoir context.
- Explain the three clinical stages and their organ-system manifestations.
- Trace innate immunity, antibody responses, and bacterial immune evasion.
- Correlate skin, joint, vascular, and nervous-system pathology with diagnosis.

Spirochetes: Organism-level context



Schematic bacterial outline — not a photomicrograph

Structural features

Slender, helical bacteria

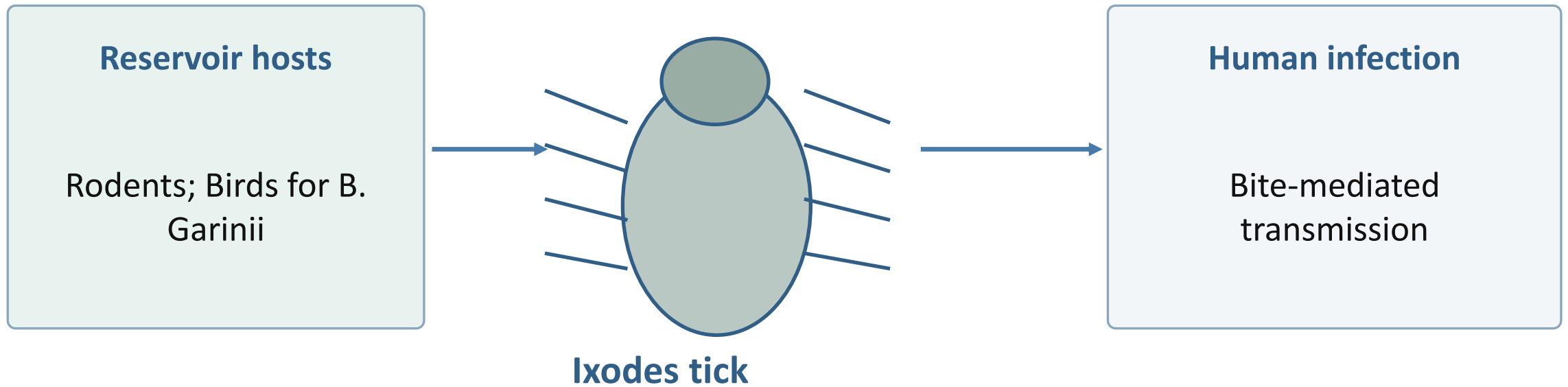
Axial periplasmic flagella

Outer sheath around the protoplasm

Borrelia species: Geographic associations

Organism	Association
B. Burgdorferi	Principal species in the United States
B. Afzelii	Additional cause in Europe and Asia
B. Garinii	Additional cause in Europe and Asia

Reservoir → Ixodes tick → human



Transmission schematic; The host associations follow Robbins.

Endemic distribution is geographically clustered

- Lyme disease is endemic in the United States, Europe, and Asia.
- The northeastern United States and upper Midwest are emphasized.
- The distribution of Lyme arthritis is described as expanding.
- Geographic exposure informs the interpretation of compatible clinical findings.

Epidemiologic figures require temporal context

Older reported-case estimate

30,000–40,000 US reports per year over several years

Textbook notes this may be only 10% of persons treated

Interpretive caution

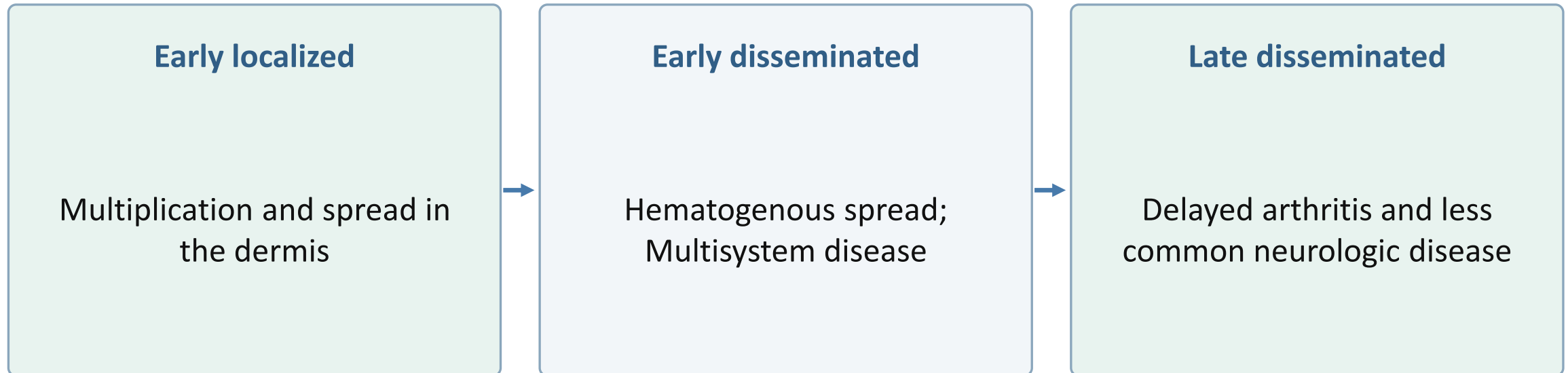
These are historical figures quoted by Robbins.

They are not presented as a current surveillance estimate.

Tick coinfections: A separate diagnostic consideration

- In some endemic areas, *B. Burgdorferi* in up to 50% of ticks.
- The same *Ixodes* ticks may harbor *Ehrlichia* spp. And *Babesia* spp.
- Coinfection possibility should not be confused with a defining feature of Lyme disease.
- Do not infer individual infection probability from the proportion of ticks infected.

Three-stage natural history

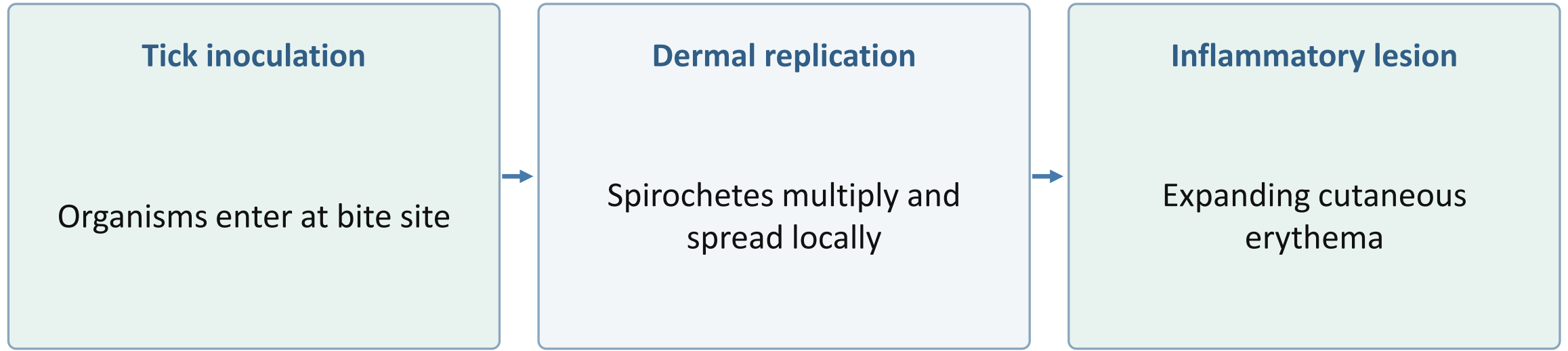


Clinical stages are descriptive; Organ manifestations can overlap.

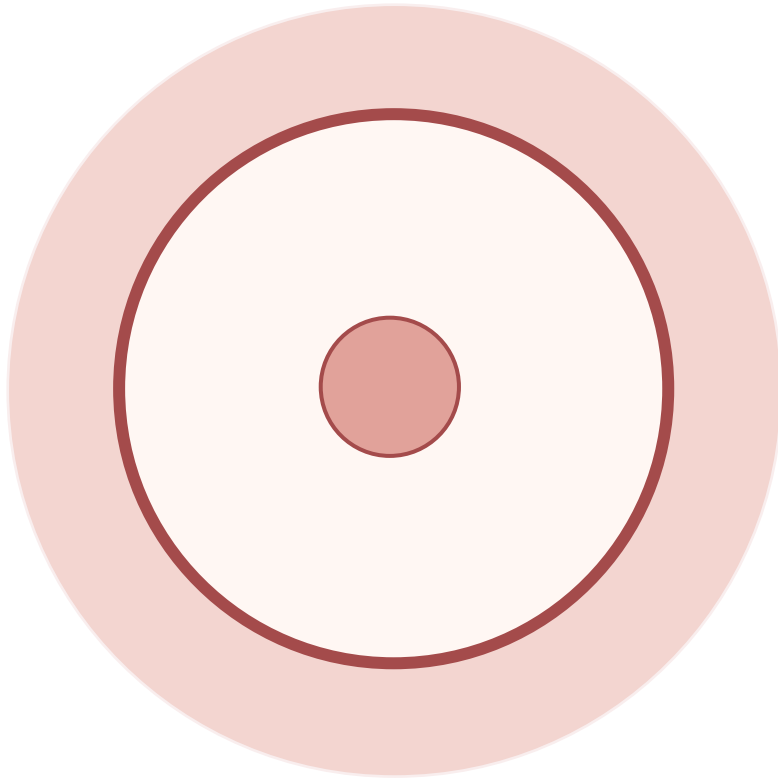
Clinical stage versus dominant manifestations

Phase	Dominant teaching features
Early localized	Erythema migrans; Fever or lymphadenopathy
Early disseminated	Secondary rash; Carditis; Cranial neuropathy; Meningitis
Late disseminated	Large-joint arthritis; Occasional neuropathy or encephalitis

Initial dermal infection explains early rash



Erythema migrans: Expanding cutaneous lesion



Simplified morphology schematic — not a clinical photograph

Characteristic pattern

Expanding erythematous area

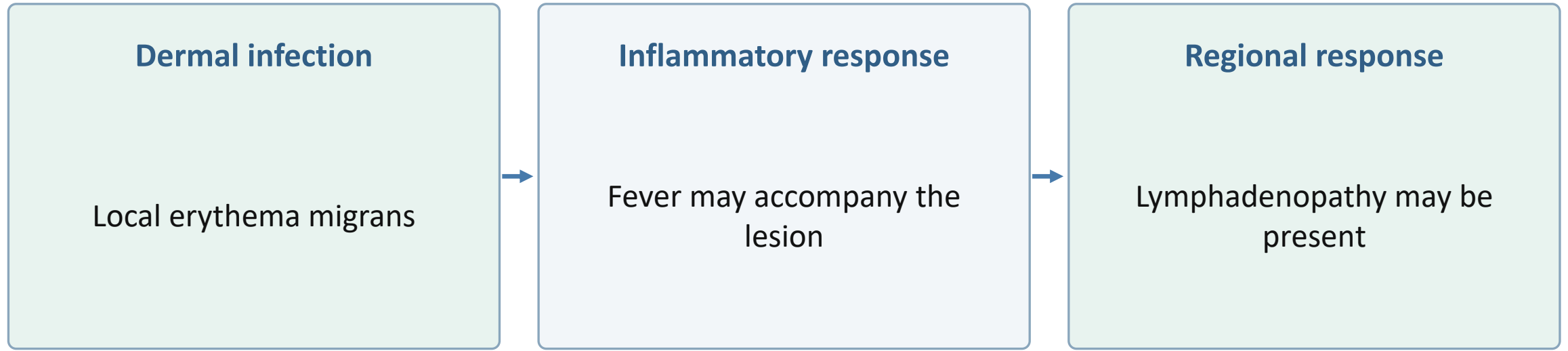
Central pallor may occur

Often appears at the tick-bite site

Erythema migrans is a frequent early sign

- Erythema migrans in approximately 80% of patients.
- The lesion often expands and may have a paler central region.
- Fever and lymphadenopathy can accompany the skin finding.
- A ring-like appearance is typical but is not required by the source description.

Local disease: Lesion and systemic symptoms

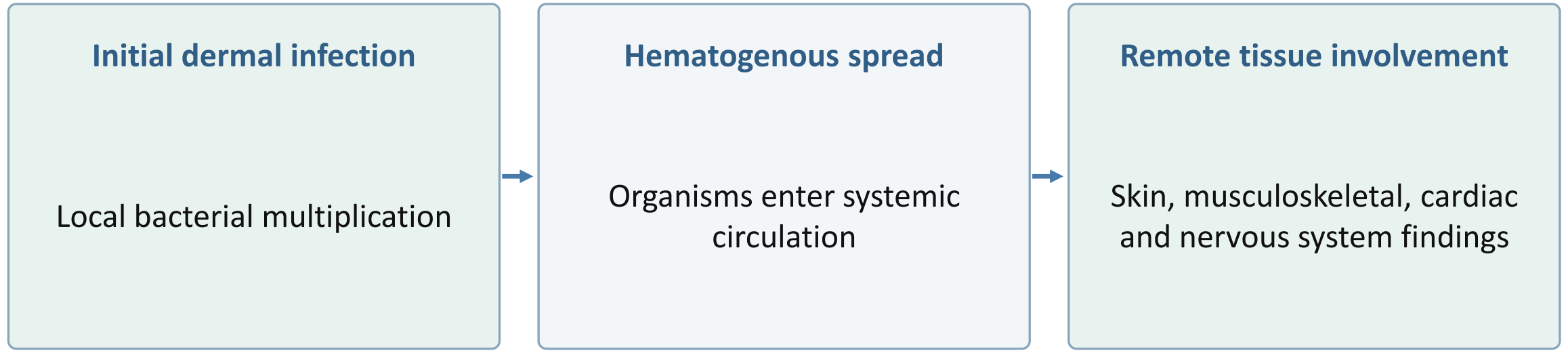


Interpret rash, systemic symptoms, and tick exposure together.

Spontaneous fading does not define microbial eradication

- Erythema migrans resolves in 4–12 weeks.
- Visible improvement of the skin lesion is distinct from elimination of infection.
- The natural history includes potential subsequent dissemination.
- The stage sequence is a disease framework, not a patient-specific prediction.

Early dissemination occurs through the bloodstream



Skin findings: Localized versus disseminated

Early localized

Primary expanding erythema migrans

Initial bite-site lesion

Early disseminated

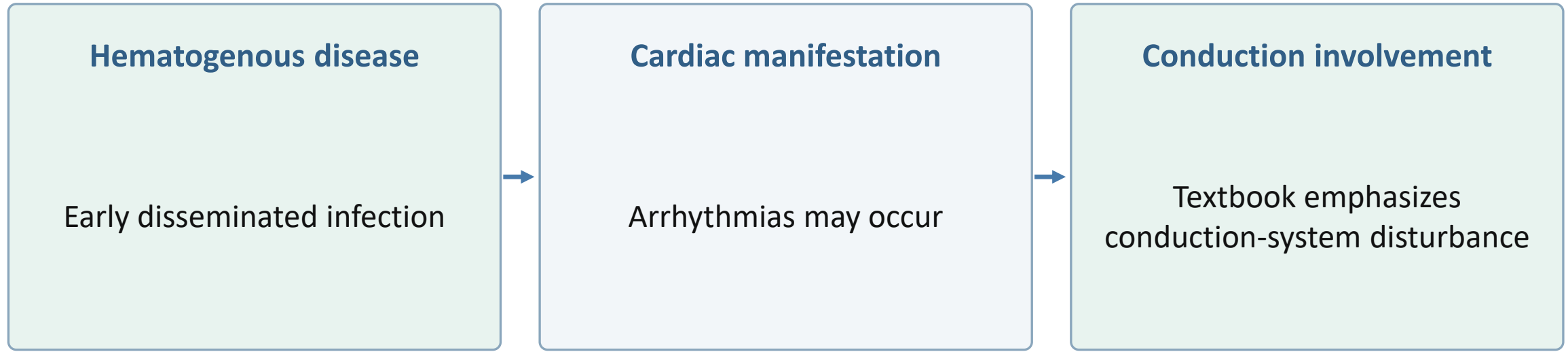
Secondary cutaneous lesions

May occur with systemic symptoms

Early disseminated musculoskeletal symptoms

- Migratory joint pain can accompany systemic spread.
- Migratory muscle pain is also reported.
- These complaints should be distinguished from later established chronic synovitis.
- The site and persistence of symptoms help frame the stage.

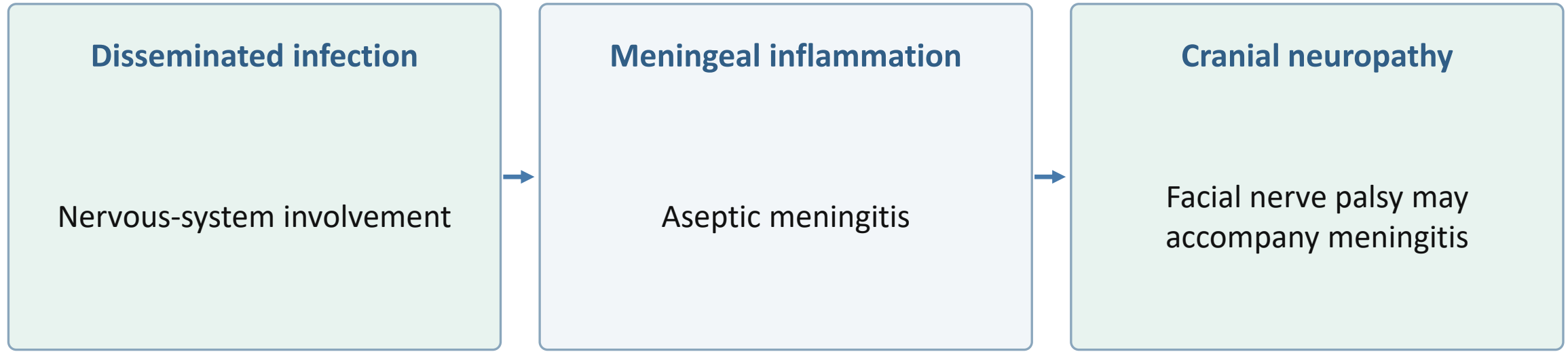
Cardiac involvement during dissemination



Lyme carditis: Conduction disturbances

- The cardiac Robbins section reports myocarditis in approximately 5% of patients.
- Its principal clinical expression is a usually self-limited conduction-system disorder.
- Some presentations may require temporary cardiac pacing.
- This figure is a textbook estimate, not a verified current population rate.

Neuroborreliosis: Meninges and cranial nerves



Facial neuropathy may be unilateral or bilateral

- Cranial nerve involvement in disseminated disease.
- Peripheral nerve material specifies unilateral or bilateral facial nerve palsies.
- Associated polyradiculoneuropathy is primarily axonal in the source.
- Cranial neuropathy and meningeal involvement need not be mutually exclusive.

Borrelial lymphocytoma: Uncommon regional manifestation

Clinical pattern

Associated with *B. Afzelii* in Europe

Blue-to-red swelling

Earlobe in children; Nipple in adults

Pathologic correlate

Lymphocytic infiltration of the lesion

Distinctive but uncommon manifestation

Not equivalent to erythema migrans

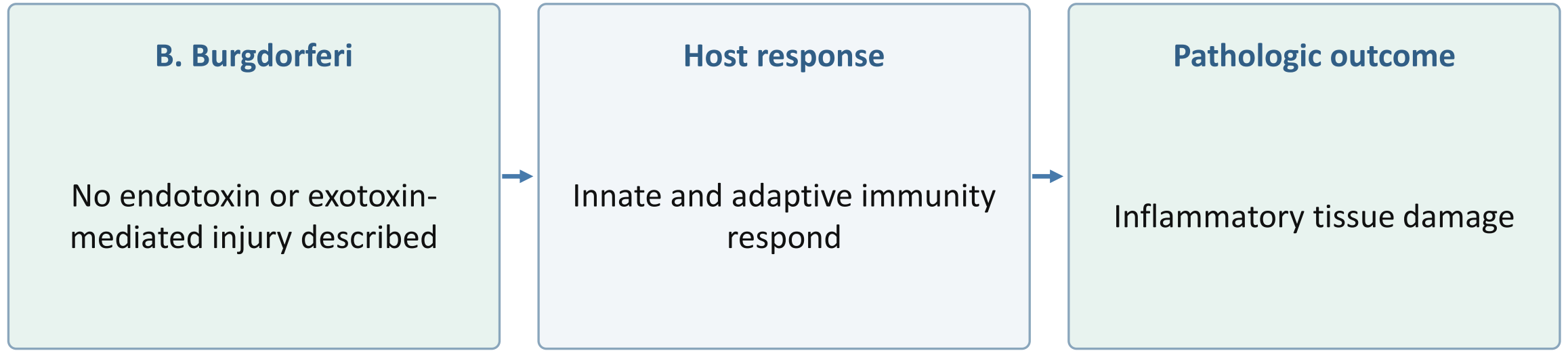
Early dissemination is multisystem

System	Reported manifestation
Skin	Multiple / secondary cutaneous lesions
Musculoskeletal	Migratory arthralgia and myalgia
Heart	Arrhythmia or conduction disturbance
Nervous system	Meningitis and cranial neuropathy

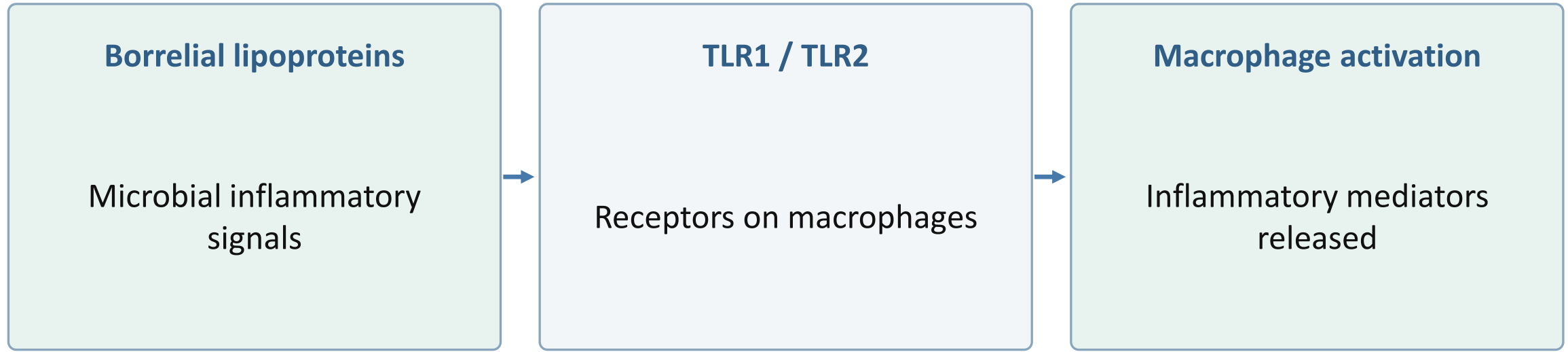
Late disseminated disease can emerge after months

- Late manifestations may appear many months after the tick bite.
- Chronic arthritis is a defining late complication.
- Progression can damage cartilage in large joints.
- Neurologic manifestations are less common but sometimes disabling.

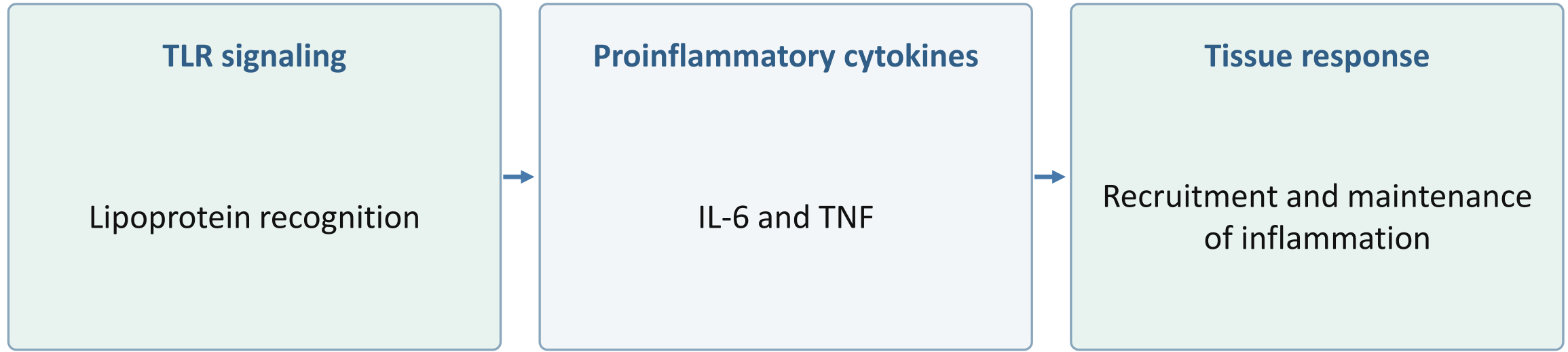
The dominant tissue-injury mechanism is inflammatory



Bacterial lipoproteins activate innate receptors



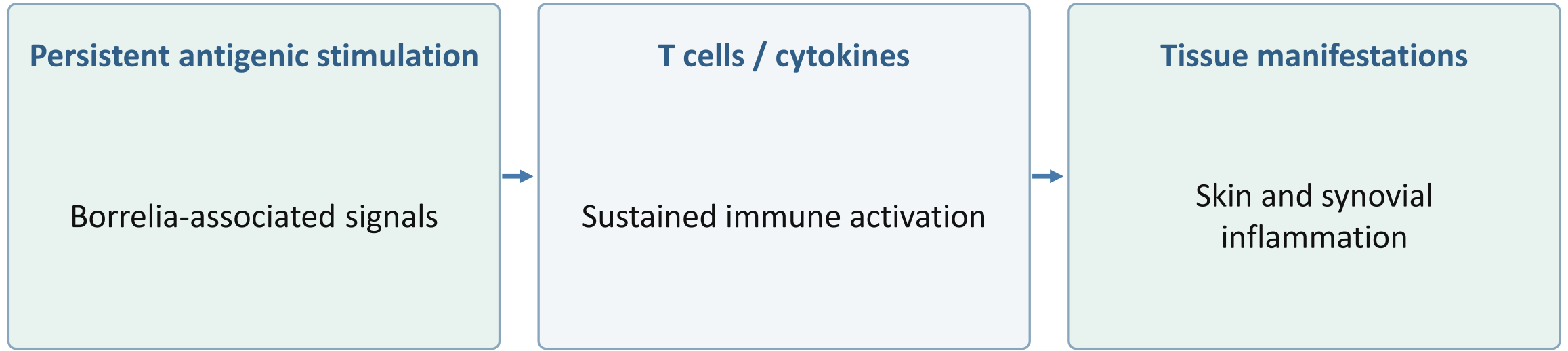
Activated macrophages amplify inflammation



Innate responses reduce burden without reliably clearing infection

- Macrophages generate bactericidal reactive nitrogen intermediates.
- The initial host response usually lowers microbial burden.
- That the response often fails to eradicate the organism.
- Persistence therefore coexists with an active inflammatory response.

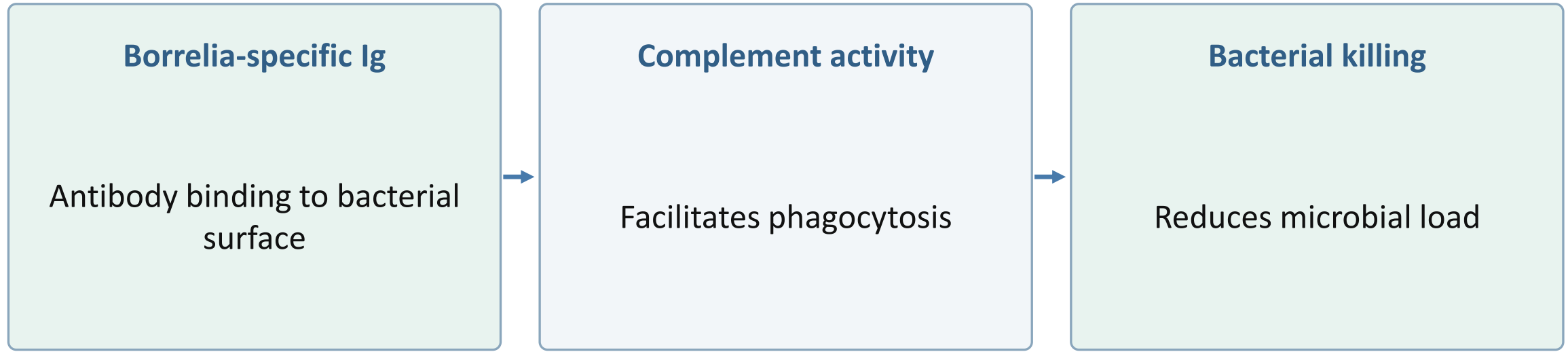
T-cell and cytokine responses drive lesions



Borrelia-specific humoral immunity develops later

- Specific antibodies appear about 2–4 weeks after infection.
- These antibodies can promote complement-mediated opsonophagocytic killing.
- Humoral immunity limits infection but does not guarantee elimination.
- The antibody timeline gives context to serology-based diagnosis.

Complement-assisted bacterial clearance



Immune defense versus bacterial persistence

Host protection

Macrophage cytokine response

Reactive nitrogen intermediates

Complement-assisted killing

Bacterial escape

Changes in VlsE antigenic identity

Downregulation of surface protein C

Outer surface protein C has stage-dependent expression

- Outer surface protein C (OspC) is needed for establishing infection.
- It is not required for persistence.
- The organism can downregulate OspC as part of immune escape.
- Loss of a previously targeted surface epitope can reduce antibody recognition.

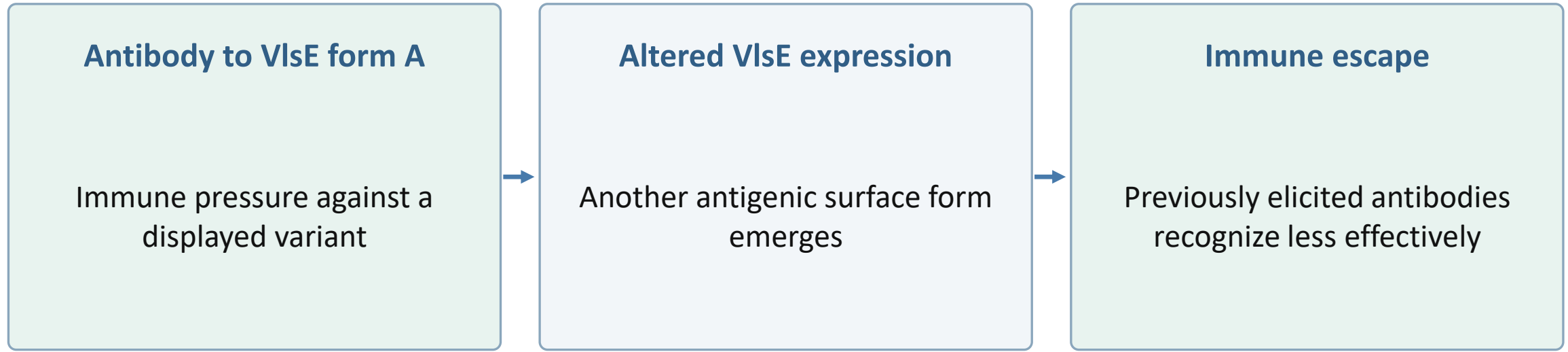
VlsE antigenic variation: Genetic architecture

Schematic: One promoter region and alternative VlsE sequence cassettes



Approximately 15 coding sequences; This figure shows only illustrative alternatives.

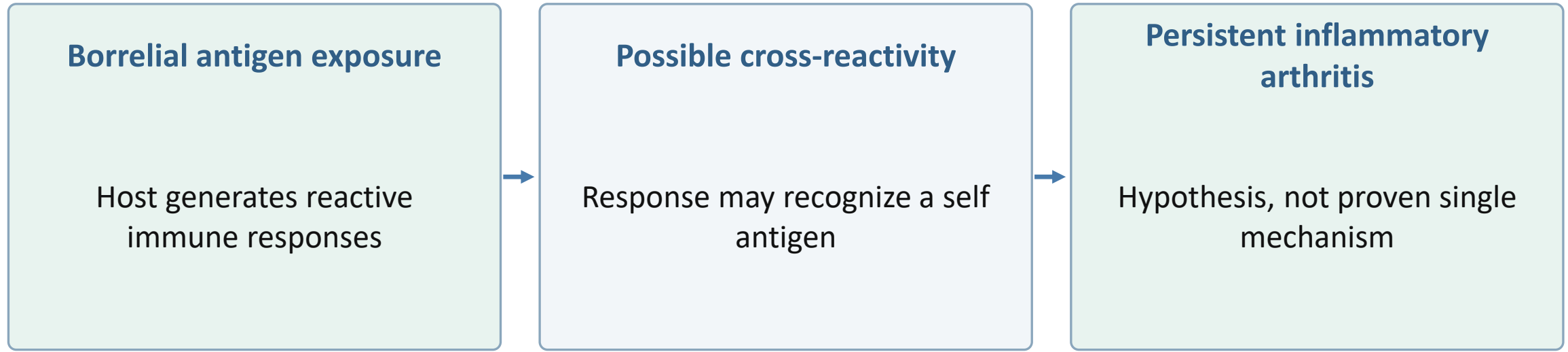
Antigenic switching can outpace an antibody response



VlsE variation is a mechanism for microbial persistence

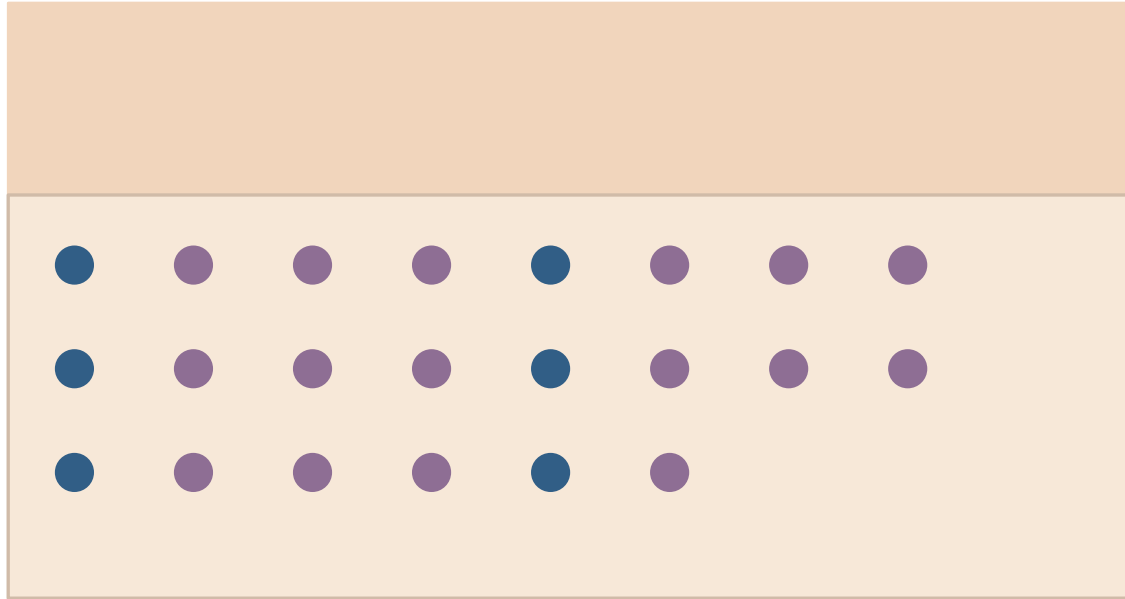
- VlsE is an antigenic surface protein.
- Alternative coding sequences can be expressed at a promoter-associated position.
- The host may recognize one variant while another escapes.
- This provides a source-supported explanation for persistent infection.

Proposed immune cross-reactivity in chronic disease



Robbins explicitly treats this autoimmune explanation as a proposal.

Skin biopsy: Edema and chronic inflammation



Microscopic findings

Dermal edema

Lymphocytic infiltrates

Plasma cells in the infiltrate

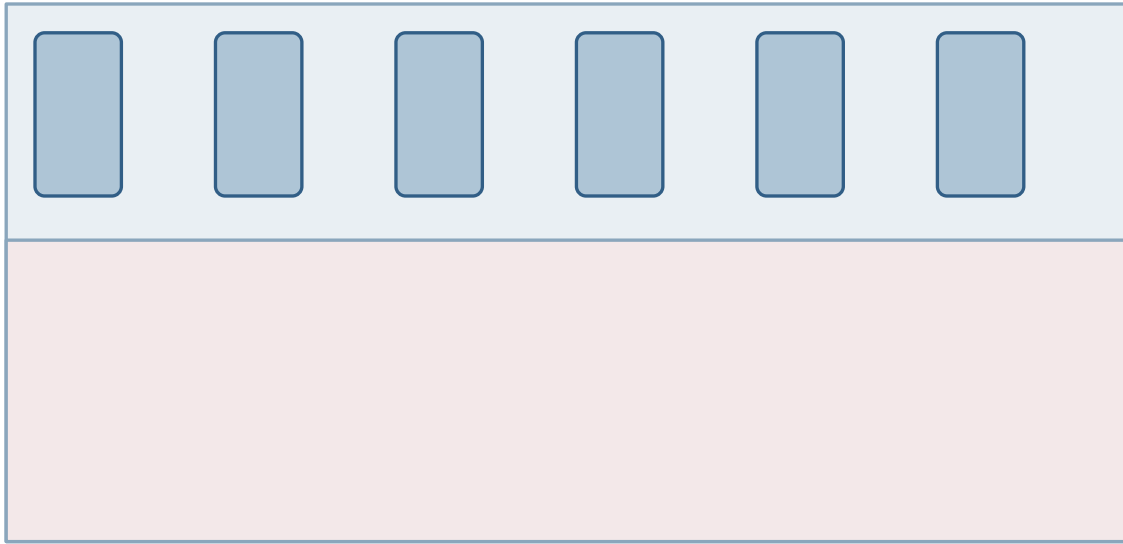
Original native schematic of dermis — not histology

Dermal findings correlate with the expanding rash

- Edema is a recorded pathologic component of Lyme skin lesions.
- Inflammatory cells include lymphocytes and plasma cells.
- This source description is not a substitute for an authentic skin photomicrograph.
- The rash is an inflammatory tissue response to local infection.

Synovial hypertrophy: Architecture of early arthritis

Villous synovial projections



Schematic architecture — not an H&E section

Early Lyme synovitis

Villous hypertrophy

Synovial lining-cell hyperplasia

Subsynovial inflammatory cells

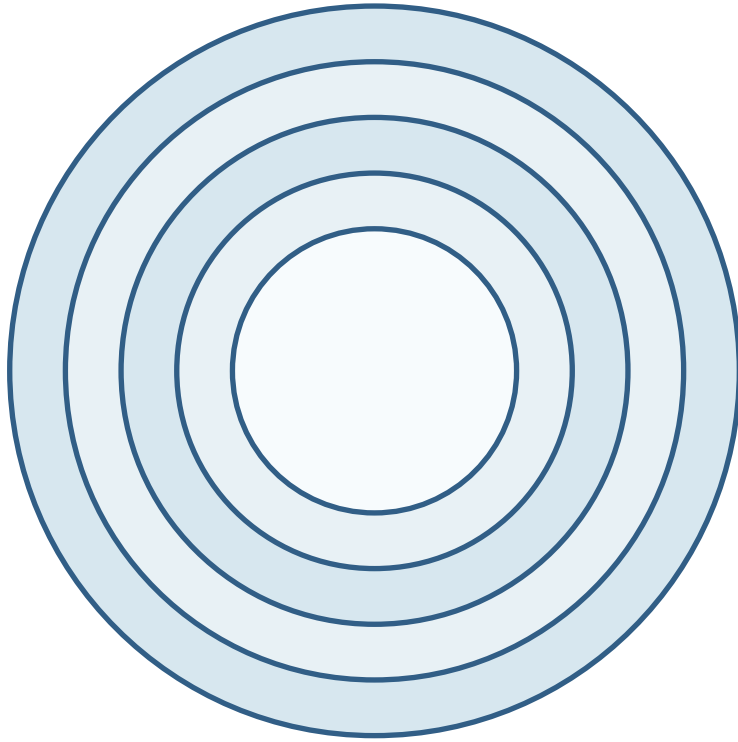
Villous hypertrophy enlarges the inflamed synovium

- The early synovium can form prominent villous projections.
- The synoviocyte lining becomes hyperplastic.
- The tissue architecture can resemble early rheumatoid arthritis.
- Microscopy must be interpreted with clinical and microbiologic context.

Cellular infiltrates in Lyme synovitis

- Abundant lymphocytes are present in the subsynovium.
- Plasma cells accompany the chronic inflammatory infiltrate.
- Chapter 26 additionally emphasizes mononuclear cells, especially CD4⁺ T cells.
- Fibrin deposition may be seen in infected synovium.

Onion-skin arteriolar change: Original schematic



Concentric arteriolar wall thickening

Pathology interpretation

Arteritis with onion-skin–like change

Chapter 26 describes obliterative endarteritis

Morphologic overlap with lesions described
in lupus

Arteritis is a distinctive morphologic clue

- Onion-skin–like arteriolar lesions in Lyme arthritis.
- Chapter 26 describes concentric arteriolar thickening as obliterative endarteritis.
- Similar patterns occur in other inflammatory diseases.
- The vessel change is suggestive in context, not independently specific.

Lyme synovitis and rheumatoid arthritis: Overlap

Lyme arthritis

Villous hypertrophy and lining hyperplasia

Lymphoplasmacytic / CD4⁺ inflammation

May show onion-skin arteriolitis

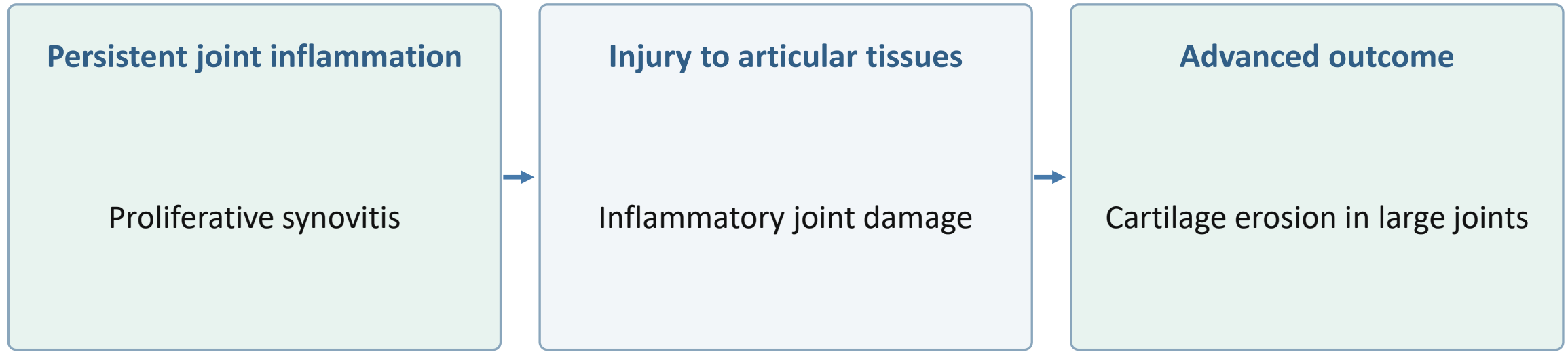
Rheumatoid arthritis

Also produces chronic proliferative synovitis

Can show villous synovial hypertrophy

Morphologic overlap limits specificity

Late joint damage emerges from chronic synovitis



Lyme arthritis: Characteristic large-joint distribution

Pattern	Textbook description
Most frequently involved	Knees
Other common joints	Shoulders, elbows, ankles
Initial attacks	Often one or two joints at a time
Course	Weeks to months; May recur elsewhere

Lyme arthritis can migrate and recur

- Initial arthritic episodes can last weeks to months.
- Only one or two large joints may be involved simultaneously.
- Subsequent episodes can occur in different joints.
- Joint pain in early dissemination is not identical to advanced synovial damage.

Treatment-era context changes the arthritis burden

Without timely treatment

Migratory arthritis in up to 80% of untreated individuals.

The figure describes the classic natural history.

Earlier treatment in practice

The same source reports arthritis in less than 10% of infections in the treatment era.

These are source-specific estimates.

Serology is the main diagnostic method

- Serologic testing as the principal diagnostic approach.
- Interpret serologic evidence in the clinical and exposure context.
- The source documents antibody generation after approximately 2–4 weeks.
- A serologic result is not an anatomical map of active organisms.

Serology and PCR answer different questions

Method	Detects / role	Limitation from source
Serology	Host anti-Borrelia antibodies	Does not localize organisms in a tissue
PCR of tissue	Borrelial DNA in sampled material	Depends on sampling of infected tissue
Synovial PCR	Borrelial DNA in joint fluid	May be negative in postinfectious arthritis

PCR in Lyme arthritis: Contextual interpretation

- Chapter 26 reports detectable *Borrelia* DNA in synovial fluid in about 70% of patients with Lyme arthritis.
- This is a textbook figure, not a current assay performance specification.
- PCR positivity demonstrates detectable target DNA in the sampled specimen.
- Robbins still describes serology as the usual basis of diagnosis.

Persistent arthritis: Infection versus postinfectious process

Active Lyme arthritis

Arthritis in *Borrelia* infection

Synovial PCR may detect organismal DNA

Antibiotic therapy is usually effective

Postinfectious arthritis

Uncommon persistence after antibiotic treatment

Organism frequently undetectable by PCR

Immune-mediated mechanism proposed

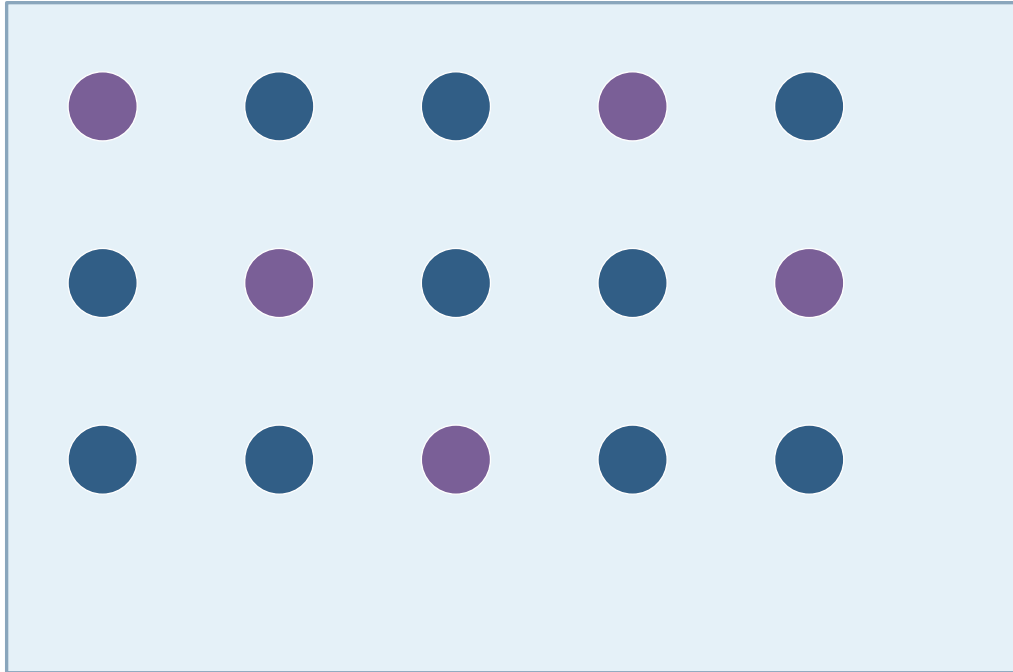
Postinfectious Lyme arthritis is not proof of persistence

- A minority have persistent joint inflammation after therapy.
- In many such patients *Borrelia* is not detected, even by synovial PCR.
- Cross-reactive immune injury as one possible explanation.
- Persistent symptoms and detectable viable spirochetes must not be assumed equivalent.

Treatment outcome as reported

- Chapter 26 reports approximately 90% cure with antibiotics active against *Borrelia*.
- Treatment often prevents the development of late arthritis.
- Postinfectious inflammatory manifestations may require a separate conceptual framework.
- This pathology lecture does not specify drug regimens or treatment durations.

Lyme meningitis: A lymphoplasmacytic CSF response



CSF: Elevated cells (schematic only)

Reported CSF features

Hypercellularity

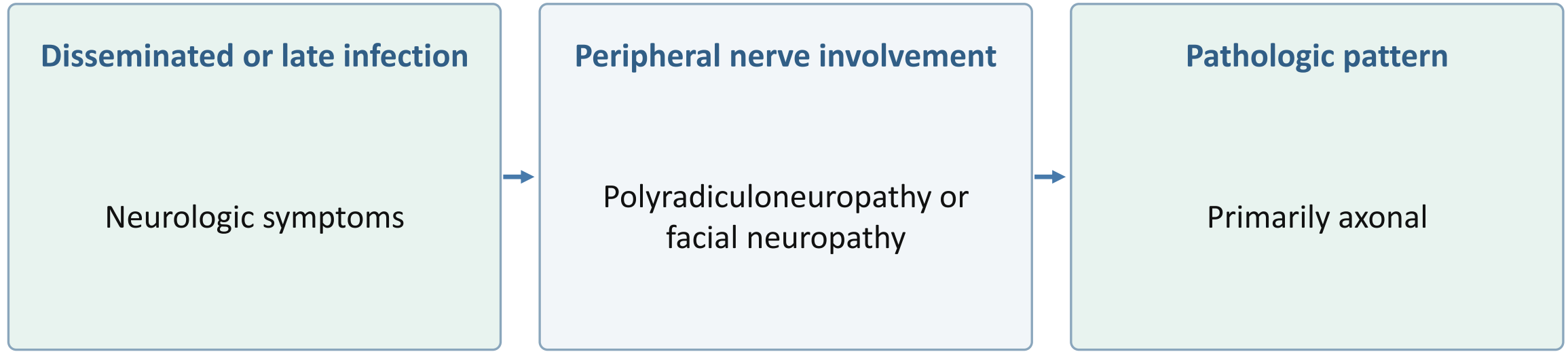
Lymphoplasmacytic infiltrate

Antispirochete IgG may be present

Neurologic disease spans several compartments

- Aseptic meningitis is a recognized nervous-system presentation.
- Facial nerve palsy and polyneuropathy can occur.
- Encephalopathy is noted in the central nervous system chapter.
- Disease severity ranges from mild to disabling.

Peripheral neuroborreliosis: Axonal neuropathy



Autopsy evidence is rare and limited

- The CNS chapter emphasizes that autopsy cases are unusual.
- Reported findings include focal microglial-cell proliferation.
- Scattered extracellular organisms have been described.
- These findings should not be represented as routine biopsy criteria.

Compartment-level clinicopathologic comparison

Site	Dominant manifestation	Pathology / correlate
Skin	Erythema migrans	Dermal edema; Lymphocytes and plasma cells
Synovium	Chronic large-joint arthritis	Lining hyperplasia; Arteritis; Fibrin
CSF / meninges	Meningitis	Lymphoplasmacytic cellular response
Heart	Conduction disturbance	Carditis / myocarditis
Peripheral nerves	Facial palsy / radiculoneuropathy	Predominantly axonal pattern

Case application: An expanding rash

Hypothetical teaching case

A person living in an endemic region notices an enlarging erythematous lesion after a possible tick exposure. Fever and regional lymph-node enlargement are also present.

Which phase is most compatible with these findings?

Case reasoning: Early localized infection

- The expanding primary skin lesion supports erythema migrans.
- Fever and lymphadenopathy are compatible accompanying signs.
- The stage reflects local dermal multiplication and spread.
- Do not equate fading of the rash with assured organism elimination.

Case application: Episodic large-joint swelling

Hypothetical teaching case

A patient with a prior compatible tick-associated illness has recurrent episodes of knee swelling months later. Synovial inflammation is present; The clinician is evaluating for Lyme arthritis.

Which tissue features and tests are most informative?

Case reasoning: Chronic inflammatory synovitis

- Expect villous hypertrophy, lining-cell hyperplasia and mononuclear infiltrates.
- An onion-skin arteriolar lesion is a distinctive associated feature.
- Serology is the usual diagnostic method; Synovial PCR can provide additional evidence.
- Persistent symptoms after antibiotics do not alone prove continued infection.

Case application: Meningeal and facial involvement

Hypothetical teaching case

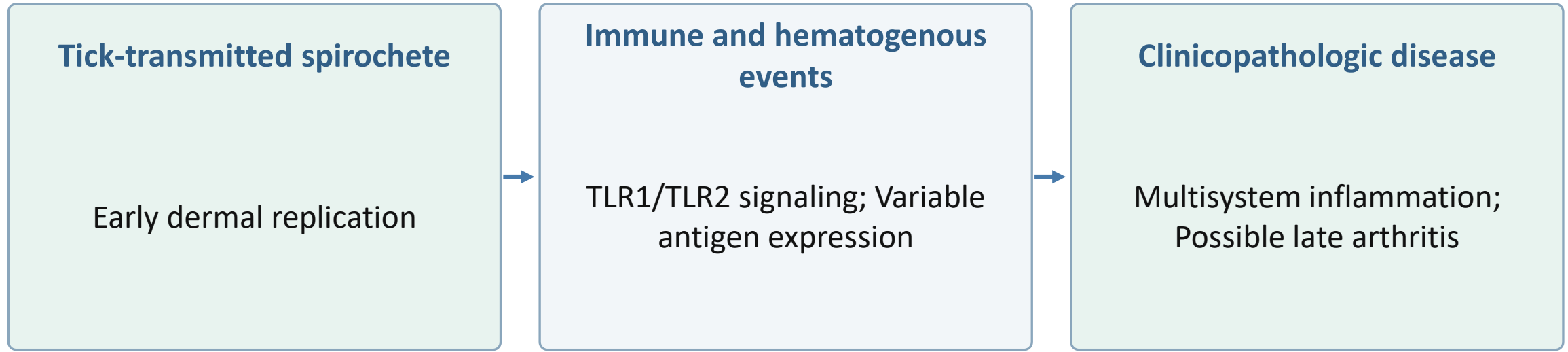
A patient develops lymphocytic meningitis together with unilateral facial weakness during an illness compatible with disseminated Lyme disease.

Explain the likely organ distribution and stage.

Case reasoning: Neuroborreliosis

- The clinical combination supports early disseminated neurologic involvement.
- Meningeal inflammation and cranial neuropathy are both.
- Lyme CSF may be hypercellular and contain antispirochete IgG.
- The peripheral neuropathy described is mainly axonal.

Integrated sequence: Infection → host injury → late effects



Mechanistic synthesis: Three essential distinctions

Question	Evidence-supported answer
How does tissue injury occur?	Mainly host inflammation; Not Borrelial endotoxin or exotoxin
How may bacteria persist?	OspC downregulation and VlsE antigenic variation
Why may arthritis persist after therapy?	A cross-reactive autoimmune mechanism is proposed, not proven

Lyme disease: Five defensible conclusions

- Ixodes-transmitted *Borrelia* infection can involve skin, heart, joints and nervous system.
- The three-stage model links local dermal disease to dissemination and late sequelae.
- Innate and adaptive immunity drive both protection and inflammatory tissue injury.
- Antigenic variation helps explain persistent infection despite antibodies.
- Lyme synovitis may mimic rheumatoid arthritis; Combine pathology and clinical testing.

Sources and scope

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

Chapter 8 Lyme Disease, pp. 344–345; Spirochete Infections, p. 341

Chapter 26 Lyme Arthritis, pp. 1093–1094

Chapter 28 Neuroborreliosis, p. 1150

Chapter 27 Peripheral nerve manifestations, p. 1112

Chapter 12 Lyme myocarditis, pp. 523–524