

Infectious Neuropathies

Patterns of peripheral nerve injury, morphology and clinicopathologic interpretation

Leprosy

Lyme disease

HIV

Diphtheria

Varicella-zoster

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Learning objectives

At the end of this lecture, interpret infectious neuropathy by linking:

Agent

Recognize the five principal infections in this unit.

Target

Identify axon, myelin/Schwann cell or sensory neuron.

Pattern

Relate distribution and symptom type to injured structures.

Morphology

Explain distinguishing tissue findings and limitations.

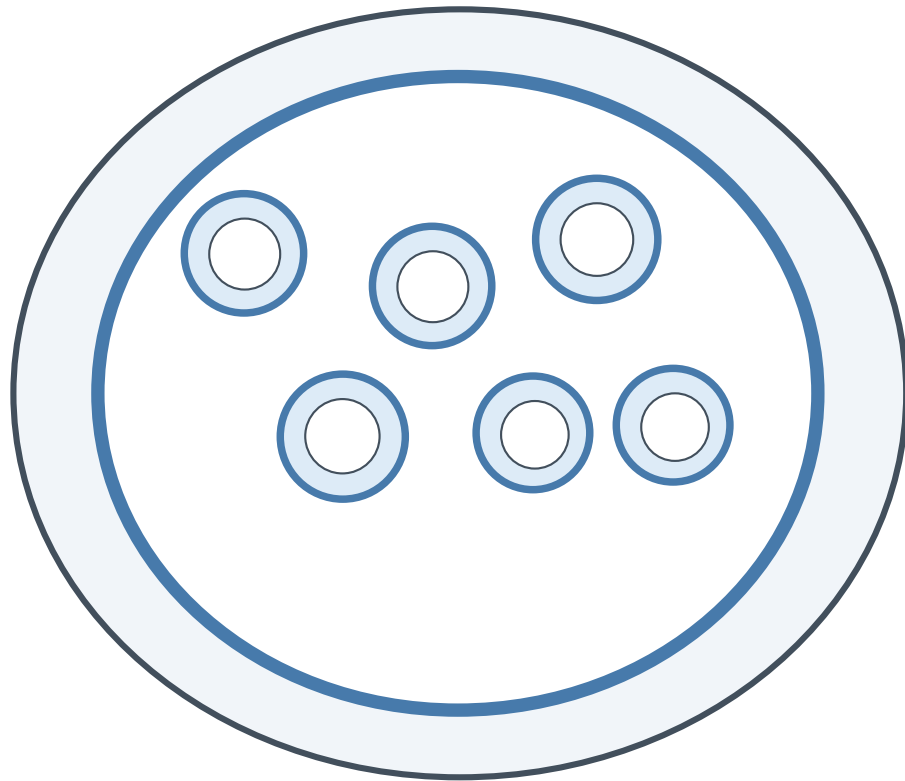
Five infectious causes, different neural targets

Infection is an etiologic category—not a single neuropathic mechanism.

Infection	Characteristic nerve involvement
Leprosy	Schwann-cell invasion or granulomatous injury
Lyme disease	Predominantly axonal radiculoneuropathy / cranial neuropathy
HIV infection	Variable patterns; later painful distal sensory axonopathy
Diphtheria	Exotoxin-associated acute demyelination
Varicella-zoster	Sensory-ganglion neuronal injury and axon loss

Where injury occurs in a peripheral nerve

Anatomic localization explains the later distribution of clinical deficits.



Schematic cross-section

Epineurium

Outer fibrovascular cover

Perineurium

Fascicular sheath

Endoneurium

Surrounds individual fibers

**Axon + Schwann
cell**

Primary functional units

Three fundamental forms of nerve injury

The initial injury target determines downstream tissue changes.

Axonopathy

Primary axonal injury;
Secondary breakdown of
associated myelin.

Demyelination

Schwann-cell/myelin damage
with relative early axonal
preservation.

Neuronopathy

Sensory neuron death
followed by degeneration of
its peripheral axon.

Axonal versus demyelinating physiology

Morphology and electrophysiology answer related but different questions.

Axonal injury

- Progressive loss of functioning axons
- Reduced response amplitude
- Velocity relatively preserved in surviving fibers

Demyelination

- Interrupted myelin internodes
- Reduced conduction velocity
- Signal amplitude may initially be preserved

Describe the distribution before naming the agent

A pattern narrows the relevant differential diagnosis.

Mononeuropathy

One named nerve and its restricted functional territory.

Polyneuropathy

Multiple nerves, often symmetric and distal.

Mononeuritis multiplex

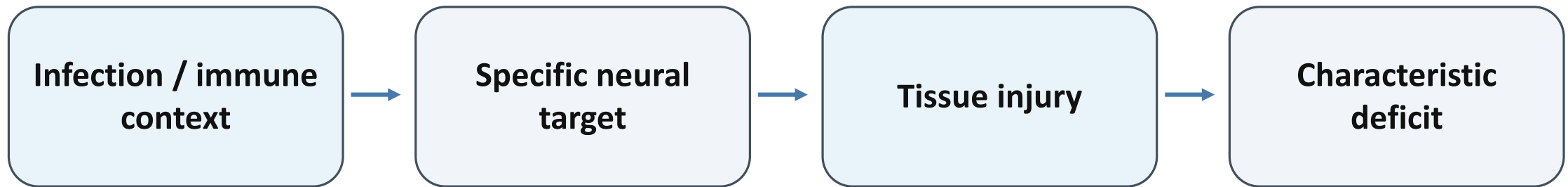
Patchy involvement of separate named nerves.

Polyradiculoneuropathy

Roots plus peripheral nerves; Proximal and distal deficits.

Mechanistic map of infectious neuropathies

Four distinct routes from an infectious process to nerve dysfunction.



- Leprosy: Cell invasion or granulomatous neuritis
- Diphtheria: Toxin-associated demyelination
- VZV: Sensory-ganglion destruction

Schematic

Leprosy: Host response determines the nerve lesion

Hansen disease prominently involves skin and peripheral nerves.

Agent

M. Leprae: Intracellular infection

Neural lesion

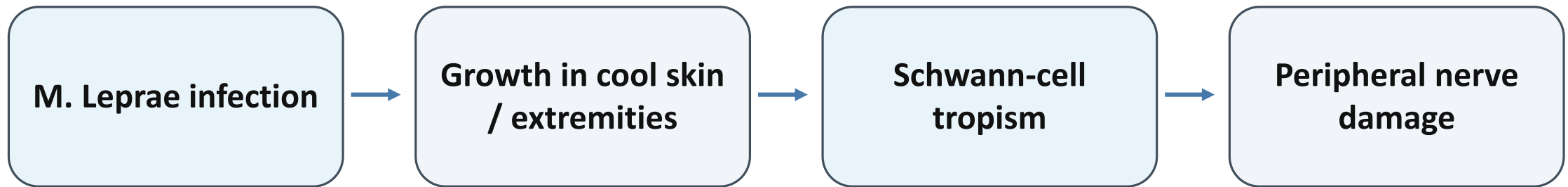
Schwann-cell invasion or
granulomatous neuritis

Consequence

Loss of pain sensation and nerve
fibrosis

Why *M. Leprae* favors peripheral nerves

Relatively cool peripheral tissues provide a favorable setting for infection.



- Organism is an obligate intracellular pathogen
- Growth favors temperatures near the skin rather than core tissues

Schematic

Leprosy is an immunologic spectrum

The same organism produces different neural pathology depending on host responses.

Tuberculoid pole

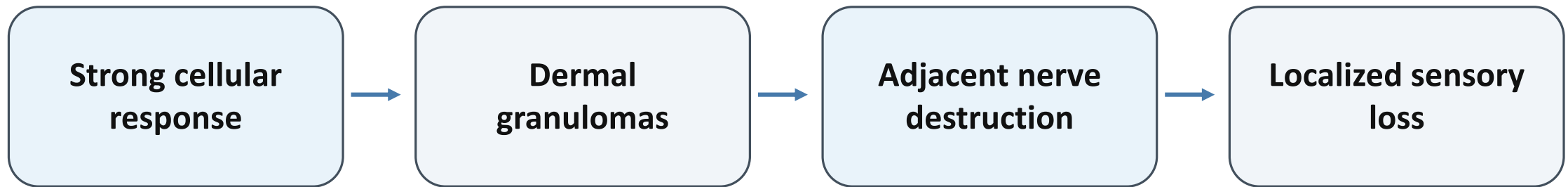
- Strong Th1 / cell-mediated immunity
- Granulomatous inflammation
- Few demonstrable bacilli

Lepromatous pole

- Weak cell-mediated control
- Numerous bacilli in tissue cells
- Widespread Schwann-cell and macrophage infection

Tuberculoid leprosy: Nerve injury by granulomatous inflammation

Immune containment of bacilli can still destroy nearby cutaneous nerves.



- Axons, myelin and Schwann cells can be lost
- Endoneurial and perineurial fibrosis may follow

Schematic

Tuberculoid skin lesions signal nerve involvement

Sensory examination is integral to pathology correlation.

Lesion

Dry, scaly or flat irregular skin lesion; Margins can be raised.

Nerve injury

Small nerve twigs may be engulfed or destroyed by granulomas.

Function

Localized sensory loss creates vulnerability to unnoticed injury.

Tuberculoid histology: Granulomas, paucibacillary tissue

Organism scarcity is not evidence against the entity when the immune response is strong.

What may be seen

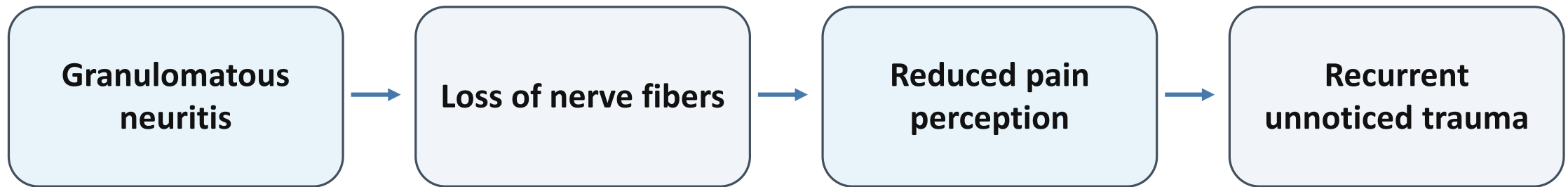
- Granulomas near or involving dermal nerves
- Loss of peripheral nerve elements
- Endoneurial/perineurial scarring

What may be difficult

- Finding acid-fast bacilli
- Proving infection from a nerve section alone
- Distinguishing injury from other granulomatous settings without context

Tuberculoid sensory deficit has a structural basis

The sequence links a skin lesion to persistent functional disability.



- Sensory dysfunction can outlast active inflammation
- Deep ulcers are consequences of absent protective sensation

Schematic

Why tuberculoid disease is usually localized

Effective cell-mediated immunity restricts the organism but not local nerve injury.

Immunity

Robust T-cell/macrophage response controls bacillary burden.

Distribution

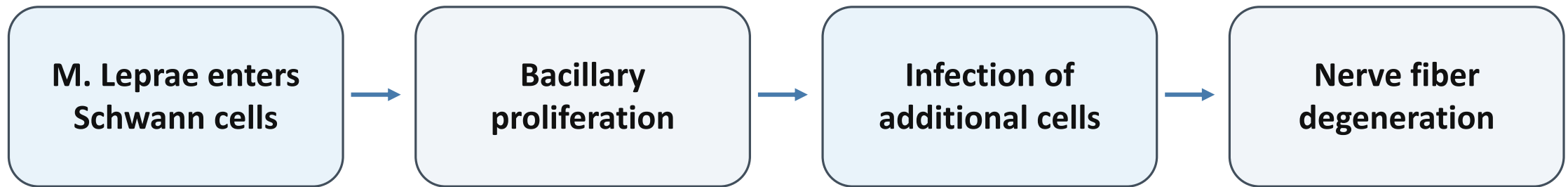
Nerve involvement is more focal than in the lepromatous pole.

Pathology

Granulomatous inflammation and fibrosis account for deficits.

Lepromatous leprosy: Direct cellular infection

Schwann cells provide an important site of peripheral nerve involvement.



- Organisms can also occur within macrophages
- Later axonal loss follows early segmental myelin injury

Schematic

Lepromatous morphology evolves over time

Early demyelination is accompanied later by structural nerve loss.

Earlier neural changes

- Schwann-cell infection
- Segmental demyelination
- Attempts at remyelination

Advanced neural changes

- Axonal degeneration
- Loss of myelinated and unmyelinated axons
- Endoneurial fibrosis; Perineurial thickening

Multibacillary pathology: What special stains reveal

Abundant organisms are a discriminator from tuberculoid disease.

Tissue cells

Foamy macrophages (lepra cells) may contain clusters of bacilli.

Staining

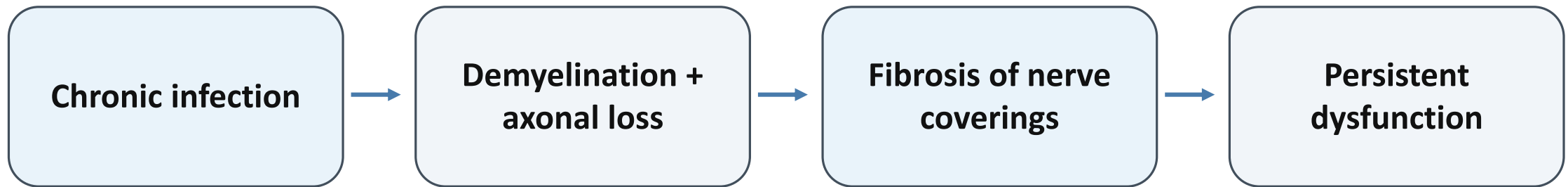
Mycobacterial stains can readily demonstrate organisms.

Neural context

Schwann cells and nerve-associated macrophages can be invaded.

Progressive scarring amplifies loss of nerve function

Perineurial and endoneurial remodeling marks advanced injury.



- Multilayered perineurial thickening is described
- Fibrosis is an endpoint—not the primary initiating event

Schematic

Why lepromatous neuropathy is distal and facial

Thermal preference helps explain its anatomical predilection.

Organism biology

M. Leprae multiplies in relatively cool tissues.

Distribution

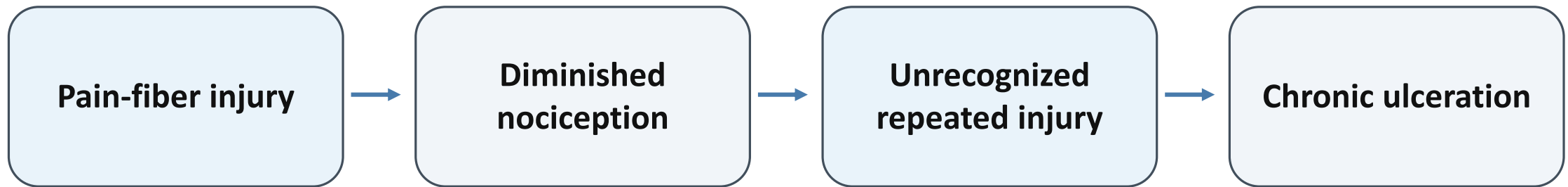
Distal extremities and the face are favored sites.

Clinical pattern

Symmetric polyneuropathy is typical of the lepromatous pole.

Small-fiber injury produces major secondary tissue damage

The most destructive visible lesions may result from loss of protection.



- Loss of pain is not a benign sensory finding
- Skin damage is secondary to peripheral nerve dysfunction

Schematic

Large superficial nerves may be clinically conspicuous

Local nerve involvement can be correlated with limb distribution.

Ulnar nerve region

- Relatively superficial near elbow
- Upper-limb sensory and motor territory
- Can be involved in lepromatous disease

Peroneal nerve region

- Relatively superficial near knee
- Lower-limb functional territory
- Can be involved in lepromatous disease

Lepromatous disease is not confined to skin

Widespread tissue distribution accompanies weak cellular control.

Skin

Diffuse thickening, macules, papules or nodules.

Peripheral nerves

Symmetric nerve invasion and sensory impairment.

Other sites

Upper airways, anterior eye, lymphoid tissue and testes may be involved.

Tuberculoid versus lepromatous: Diagnostic contrast

The immune response predicts bacillary load and neural distribution.

Tuberculoid

- Granulomatous cellular response
- Paucibacillary sections
- Localized or asymmetric neuropathy

Lepromatous

- Numerous infected tissue cells
- Multibacillary sections
- More diffuse symmetric polyneuropathy

Leprosy tissue findings should be read together

No isolated finding substitutes for clinicopathologic integration.

Finding	Interpretation	Dominant pole
Granulomas around dermal nerves	Immune-mediated nerve destruction	Tuberculoid
Bacilli within Schwann cells	Direct organism-associated neural injury	Lepromatous
Perineurial/endoneurial fibrosis	Chronic destructive process	Both
Small pain-fiber loss	Loss of protective sensation	Prominent in lepromatous

Case: Anesthetic plaque with localized nerve involvement

A patient has an insensate dry skin plaque and nearby granulomatous neuritis.

A patient has an insensate dry skin plaque and nearby granulomatous neuritis.

Which immunologic pole is most consistent with this pattern—and why might acid-fast staining be negative?

Discuss before revealing the answer

Case: Symmetric distal loss of pain sensation

A patient has diffuse nodular skin disease and recurrent painless foot ulcers.

A patient has diffuse nodular skin disease and recurrent painless foot ulcers.

Identify the proposed mechanism linking organism biology to the ulcers.

Discuss before revealing the answer

Lyme disease: Radicular and cranial neuropathies

Borrelia infection produces several stage-dependent neurologic manifestations.

Agent

Tick-borne Borrelia infection

Neural lesion

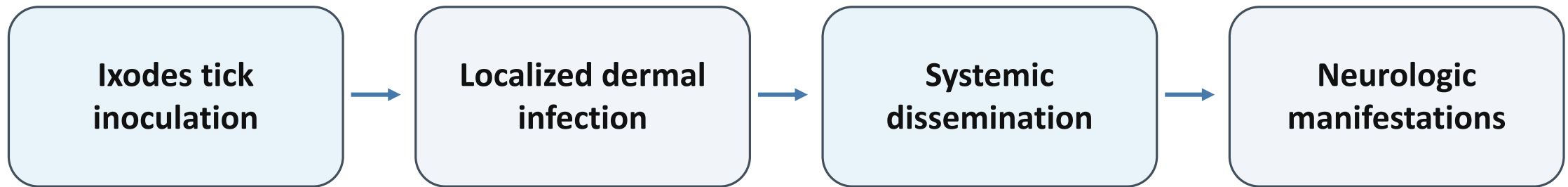
Primarily axonal radicular /
cranial injury

Consequence

Facial palsy or
polyradiculoneuropathy

From tick exposure to disseminated disease

Neurologic involvement occurs after the earliest localized skin phase.



- Borrelia species cause Lyme disease
- Cranial nerve involvement is described in early disseminated disease

Schematic

Neurologic Lyme disease is not one nerve pattern

The source describes several forms rather than a single stereotyped neuropathy.

Radicular

Polyradiculoneuropathy affecting nerve roots and peripheral nerves.

Cranial

Unilateral or bilateral facial nerve palsy.

Axonal

Neuropathic injury is described as primarily axonal.

Facial neuropathy can be unilateral or bilateral

Laterality supports pattern recognition but does not establish etiology.

Unilateral facial palsy

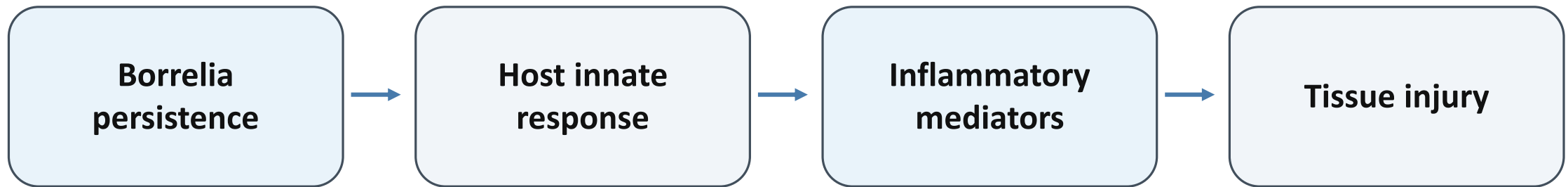
- Cranial nerve involvement is possible
- Consider stage and infectious context
- Not specific to *Borrelia* infection

Bilateral facial palsy

- Also described in Lyme disease
- Systemic context remains essential
- Do not assume a demyelinating mechanism

Immune inflammation contributes to Lyme lesions

Inflammatory responses rather than a bacterial exotoxin.



- Bacterial lipoproteins engage TLR1/TLR2
- This is systemic pathogenesis context; Neural cellular details are not specified

Schematic

Lyme stage and neurologic timing

Avoid equating late manifestations with an obligatory sequence in every patient.

Early localized

Erythema migrans at the inoculation site is characteristic.

Early disseminated

Meningitis with cranial nerve involvement may occur.

Late disseminated

Polyneuropathy can occur but is less frequent than arthritis.

Case: Cranial neuropathy after disseminated infection

A patient with compatible tick exposure develops bilateral facial weakness.

A patient with compatible tick exposure develops bilateral facial weakness.

Which infectious neuropathy in this unit specifically includes bilateral facial nerve palsies?

Discuss before revealing the answer

HIV: Immune dysregulation and multiple phenotypes

HIV-associated neuropathies change in pattern across infection stages.

Setting

HIV-associated immune
dysregulation

Neural lesion

Early multifocal / demyelinating;
Late axonal

Consequence

Often painful distal sensory
neuropathy

Why HIV neuropathy resists a single mechanism

The text associates diverse patterns with immune dysregulation.

Heterogeneous

No single anatomic neuropathy pattern covers all patients.

Mechanistic uncertainty

Pathogenesis remains incompletely understood.

Context-dependent

Earlier and later stages have different common patterns.

Earlier HIV: Two neuropathic presentations

Early infection may mimic disorders with very different distributions.

Mononeuritis multiplex

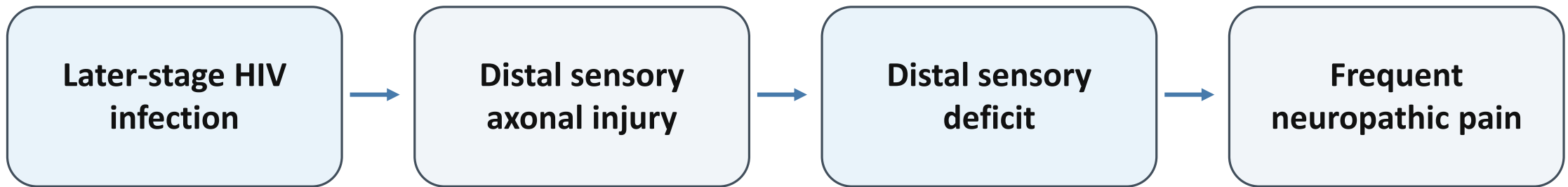
- Asymmetric, multifocal named-nerve deficits
- Pattern of scattered axonal dysfunction
- Can arise early in HIV infection

Inflammatory demyelinating

- GBS-like or CIDP-like syndromes
- May resemble immune neuropathies
- Timing and clinical pattern matter

Later HIV: A painful distal sensory axonopathy

The characteristic later pattern combines length-dependent distribution and pain.



- This is the more common described later-stage pattern
- Robbins does not specify a single definitive molecular mechanism

Schematic

HIV: Early and late nerve involvement

Stage is contextual, not an absolute diagnostic criterion.

Earlier

- Mononeuritis multiplex can occur
- Demyelinating disorders may resemble GBS/CIDP
- Variable distributions

Later

- Distal sensory neuropathy is more common
- Axonal pattern is typical
- Often painful

Interpreting painful distal HIV neuropathy

Combine symptom character with nerve-injury distribution.

Positive symptoms

Pain can accompany damaged sensory axons.

Negative symptoms

Distal loss of sensation reflects loss of functional fibers.

Important restraint

Immune dysregulation is implicated; A complete mechanism is not established here.

Case: Painful distal feet in later HIV

A person with later-stage HIV reports distal burning discomfort and numbness.

A person with later-stage HIV reports distal burning discomfort and numbness.

Which neuropathic class is most consistent with the described pattern?

Discuss before revealing the answer

Diphtheria: Toxin-mediated demyelinating neuropathy

Neural dysfunction arises from a bacterial exotoxin rather than direct nerve colonization.

Agent

C. Diphtheriae exotoxin

Neural lesion

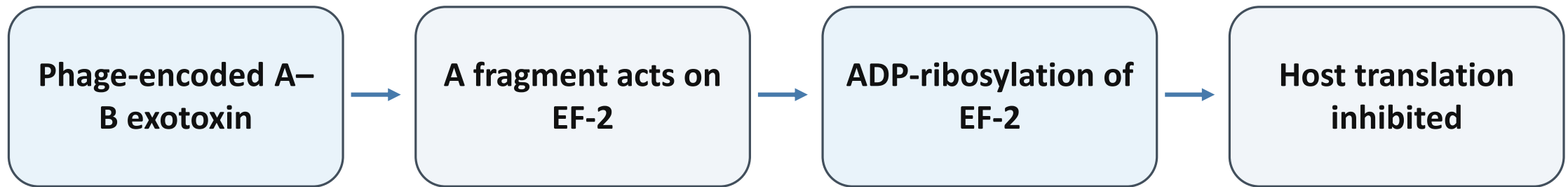
Acute demyelinating neuropathy

Consequence

Bulbar and respiratory muscle weakness

Diphtheria toxin blocks protein synthesis

A specific host molecular target.



- EF-2 is required for mRNA translation
- Neural disease is associated with systemic exotoxin effects

Schematic

Peripheral nerve injury in diphtheria

An acute demyelinating phenotype is the principal peripheral nerve lesion.

Agent

Toxigenic *Corynebacterium diphtheriae* infection.

Mediator

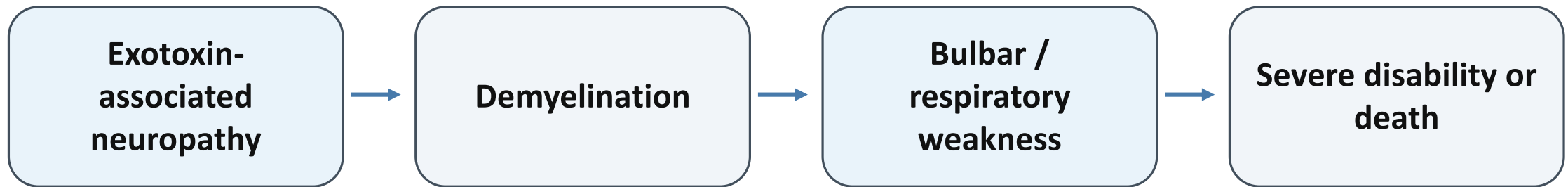
Circulating exotoxin is responsible for peripheral nerve dysfunction.

Morphology

Acute demyelination predominates.

Bulbar and respiratory dysfunction are high-stakes findings

Neural deficits can lead to life-threatening impairment.



- Prominent bulbar involvement distinguishes the clinical hazard
- This is a clinicopathologic chain—not a treatment algorithm

Schematic

Local diphtheria infection versus systemic neuropathy

The anatomic sites of organism growth and toxin effect differ.

Local infection

- Respiratory mucosa often involved
- Necrotizing pseudomembranous inflammation
- *C. Diphtheriae* replicates at mucosal sites

Peripheral neuropathy

- Driven by the released toxin
- Acute demyelinating nerve injury
- May involve bulbar/respiratory muscles

Toxoid immunization targets the actual virulence mechanism

Neutralizing antibody prevents the lethal actions of the exotoxin.

Antigen

Inactivated diphtheria toxin
(toxoid).

Protection

Antibodies neutralize the
active toxin.

Vulnerability

Incomplete immunization or
waning adult immunity can
permit disease.

Case: Acute bulbar weakness after diphtheria

A patient with respiratory diphtheria develops weakness and respiratory compromise.

A patient with respiratory diphtheria develops weakness and respiratory compromise.

What neural injury pattern should be anticipated, and what causes it?

Discuss before revealing the answer

Varicella-zoster: Sensory neuron injury and radiculoneuritis

Reactivation of latent infection links ganglion pathology to a dermatomal rash.

Setting

Reactivation after sensory ganglion latency

Neural lesion

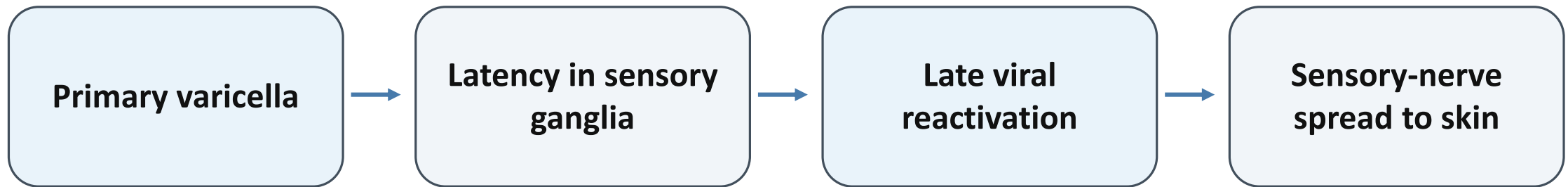
Neuronal death and secondary axon loss

Consequence

Painful dermatomal eruption ± weakness

VZV: Primary disease, latency, reactivation

Peripheral sensory ganglia connect the two clinical presentations.



- Chickenpox precedes the latent state
- Herpes zoster is a reactivation syndrome

Schematic

Why latent infection matters to neuropathy

The virus persists in a neural compartment even after the skin disease resolves.

Reservoir

Dorsal root or other sensory ganglion neurons.

Time course

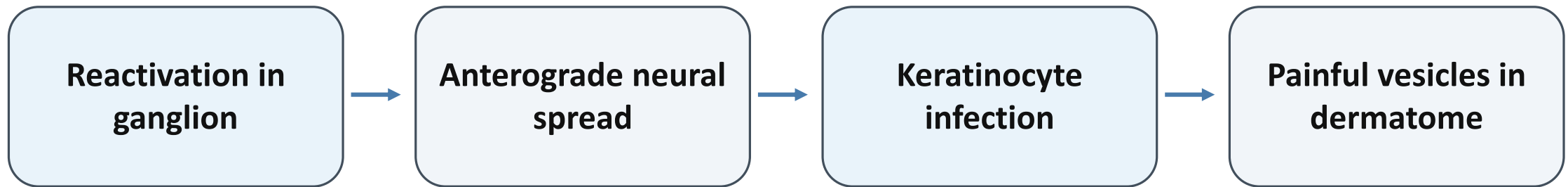
Reactivation may occur many years after primary infection.

Risk context

Reduced cell-mediated immune control is suspected to contribute.

A dermatome is the anatomical footprint of spread

Viral movement along sensory nerves explains the localized eruption.



- Thoracic and trigeminal distributions are common
- Distribution reflects innervation—not hematogenous rash spread

Schematic

Chickenpox versus herpes zoster: Different distributions

Primary and recurrent cutaneous infection have distinct pathogenesis.

Chickenpox

- Primary systemic infection
- Widespread vesicles
- Virus ultimately becomes latent in sensory ganglia

Herpes zoster

- Ganglionic reactivation
- Dermatomal vesicular eruption
- Localized neuropathic pain and radiculoneuritis

Herpes zoster pain is a neural symptom

The eruption and pain share the same segmental anatomical origin.

Radiculoneuritis

Inflammation affects sensory roots or sensory pathways.

Symptoms

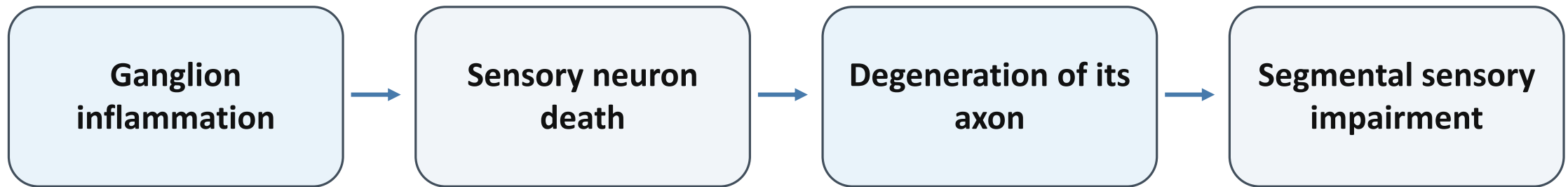
Burning, sharp pain or intense itching may accompany lesions.

Anatomy

The sensory dermatome determines the skin distribution.

Ganglion destruction explains downstream axonal loss

This is a neuronopathy rather than simply cutaneous viral infection.



- Pathology includes prominent mononuclear infiltrates
- Neuronal cell-body loss precedes secondary axonal degeneration

Schematic

VZV pathology: Ganglion versus distal nerve

The sampled compartment changes what a pathologist should expect.

Sensory ganglion

- Neuron death
- Mononuclear inflammation
- May show focal necrosis or hemorrhage

Peripheral nerve

- Axonal degeneration
- Loss of axons of affected sensory neurons
- Secondary consequence of cell-body death

A ganglion is an inflammatory lesion, not merely a reservoir

Several histologic features reflect tissue-destructive infection.

Neurons

Degeneration and death are described.

Inflammation

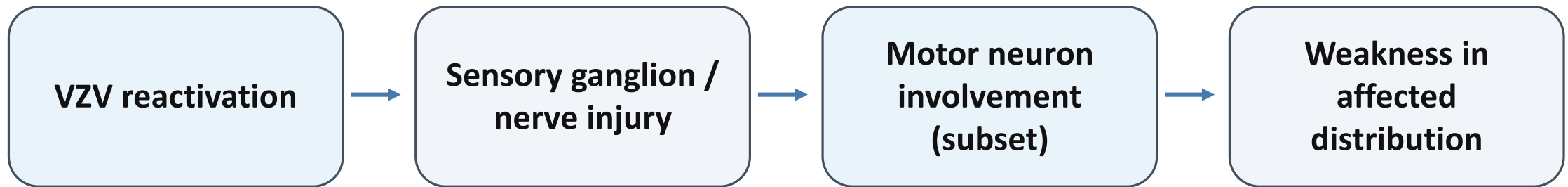
Predominantly mononuclear cell infiltrates may be abundant.

Severe injury

Focal necrosis and hemorrhage can accompany the lesion.

VZV may also affect motor systems

Segmental weakness can accompany a primarily sensory eruption.



- Anterior horn or cranial motor nuclei may show focal injury
- Motor involvement is not the dominant presentation

Schematic

Clinical localization: Thoracic and trigeminal pathways

The distribution of the eruption is part of the neurologic examination.

Thoracic

A unilateral band-like sensory distribution may localize a segment.

Trigeminal

Painful facial dermatomal involvement is common.

Rare motor syndrome

Ramsay Hunt syndrome can include facial paralysis.

VZV histology: Skin findings and neural pathology

Do not use a skin feature as a surrogate for demonstrating ganglion injury.

Skin involvement

- Vesicular keratinocyte infection
- Intraepithelial blisters and viral nuclear changes may occur
- Clinically conspicuous eruption

Neural involvement

- Sensory ganglion inflammation/neuronal death
- Axonal degeneration in downstream nerves
- CNS/peripheral morphology depends on sampled site

Varicella-zoster neuropathy: Diagnostic boundaries

Interpret findings in the correct clinical and tissue context.

Distribution

Dermatomal rash strongly supports localized reactivation.

Target

Sensory ganglion is the primary neuronal reservoir.

Histology caveat

The two Robbins chapter discussions differ on how frequently neural nuclear inclusions are encountered.

Case: Vesicles and pain in a thoracic band

An adult develops a painful vesicular eruption confined to a thoracic dermatome.

An adult develops a painful vesicular eruption confined to a thoracic dermatome.

What cell type maintains latency, and what tissue injury explains sensory deficits?

Discuss before revealing the answer

Comparative mechanisms: Which structure is injured?

Similar neuropathic symptoms arise from fundamentally different primary targets.

Disease	Principal injury mechanism	Expected pattern
Lepromatous leprosy	Schwann-cell infection → progressive axon loss	Symmetric distal neuropathy
Tuberculoid leprosy	Granulomatous cutaneous nerve injury	Focal neuropathy
Lyme disease	Infection-associated, primarily axonal	Radicular / facial cranial
HIV	Immune dysregulation; diverse patterns	Early variable, later distal sensory
Diphtheria	Exotoxin-associated demyelination	Acute, bulbar/respiratory risk
VZV	Sensory ganglion neuronopathy	Dermatomal pain ± weakness

Differentiate infection from an immune mimic

Similar clinical patterns can have distinct infectious context.

Inflammatory demyelination

- GBS and CIDP are primary immune-mediated neuropathies
- Early HIV may resemble either syndrome
- Diphtheria also produces demyelination by toxin effect

Predominant axonal injury

- Later HIV sensory neuropathy is usually axonal
- Lyme cranial/radicular injury is primarily axonal
- VZV axon loss follows ganglionic neuron death

Core morphology-to-symptom correlations

For each infection, name the primary tissue event before the clinical effect.

Lost small pain fibers

Loss of protective nociception → painless trauma and ulcers.

Demyelination

Disrupted saltatory conduction → physiologic conduction slowing.

Sensory neuron death

Distal axon degeneration → segmentally distributed deficits.

Axonal attrition

Loss of functional nerve fibers → reduced response amplitude.

Integrated case: Two opposite skin–nerve relationships

Patient A: Anesthetic plaques with granulomas; Patient B: Painful dermatomal vesicles.

Patient A: Anesthetic plaques with granulomas; Patient B: Painful dermatomal vesicles.

For each, identify the initiating neural lesion and why the symptoms differ.

Discuss before revealing the answer

Rapid pattern recognition: Five testable associations

The distinguishing feature is the linkage of organism, neural target and phenotype.

Clue	Most relevant disease	Underlying explanation
Anesthetic granulomatous patch	Tuberculoid leprosy	Immune destruction of cutaneous nerves
Acid-fast organisms in Schwann cells	Lepromatous leprosy	Cellular invasion, later fiber loss
Facial palsy ± radiculopathy	Lyme disease	Primarily axonal neuropathy
Painful distal sensory axonopathy in later disease	HIV infection	Immune dysregulation association
Bulbar weakness with demyelination	Diphtheria	Exotoxin
Painful dermatomal vesicles	VZV	Ganglionic reactivation

Primary references and source boundaries

Content follows the supplied 11th-edition Robbins text; no external criteria or fabricated imagery.

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 27: Peripheral Nerves and Skeletal Muscles, pp. 1107–1112.
- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 8: Infectious Diseases, VZV (pp. 322–323), diphtheria (p. 329), leprosy (pp. 340–341), Lyme disease (pp. 344–345).
- Pathology schematics in this presentation are original editable PowerPoint illustrations, not clinical specimens or textbook photographs.
- Chapter 27/Chapter 8 discrepancy concerning VZV ganglionic inclusions is recorded in slide notes.