

Infections Caused by Other Intracellular Bacteria

Rickettsial, oriental, ehrlichial and anaplasma infections

Mechanisms • Vascular pathology • Clinical and morphologic recognition

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Learning objectives

- Distinguish the four genera by syndrome, vector, and preferred infected cell.
- Explain how rickettsial endothelial infection produces vascular injury and systemic illness.
- Recognize typhus, scrub typhus, and spotted-fever morphology.
- Relate ehrlichiosis and anaplasmosis to leukocyte morulae and clinical presentations.

A defined group of obligate intracellular bacteria

Rickettsia

Epidemic typhus
and spotted fevers

Orientia

Scrub typhus

Ehrlichia

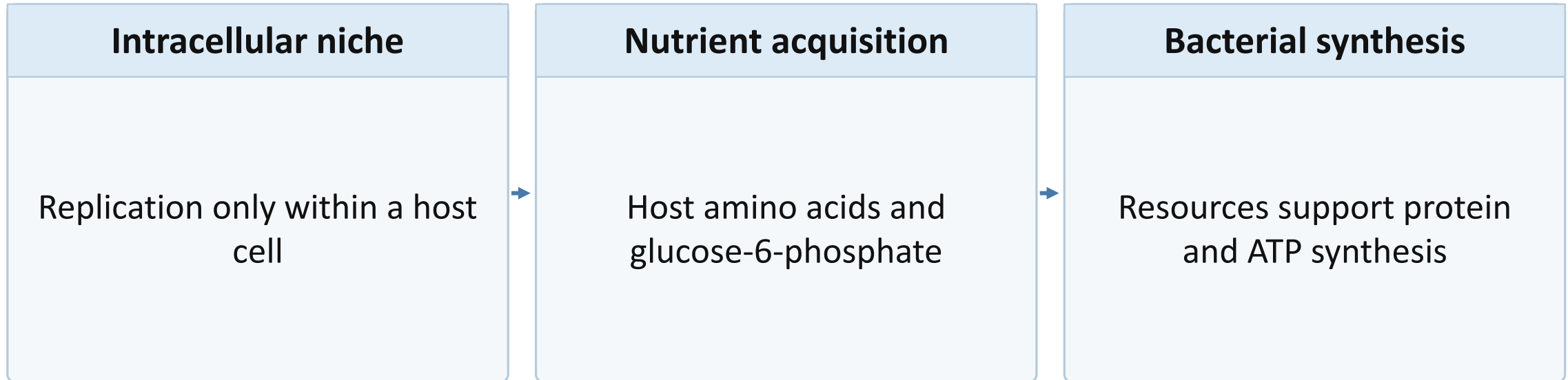
Ehrlichiosis

Anaplasma

Anaplasmosis

The shared intracellular lifestyle does not imply identical target cells or pathology.

Intracellular growth requires host cells



The host cell is both a replication compartment and a nutrient source.

Gram-negative architecture; Poor Gram-stain visibility

Bacterial structure

- Rod-shaped bacterial morphology
- Structural features of gram-negative bacteria

Routine staining caveat

- These organisms stain poorly with Gram stain.
- Failure to see organisms on a Gram stain does not exclude infection.

Vector links separate the major syndromes

Syndrome	Major organism	Transmission
Epidemic typhus	<i>R. prowazekii</i>	Body/head lice
Scrub typhus	<i>O. tsutsugamushi</i>	Chiggers (mites)
Rocky Mountain spotted fever	<i>R. rickettsii</i>	Dog ticks
Ehrlichiosis / anaplasmosis	<i>E. chaffeensis</i> / <i>A. phagocytophilum</i>	Lone star / deer ticks

The infected cell predicts the lesion

Endothelial infection

- Typhus and spotted-fever rickettsiae infect vascular endothelium.
- Vascular permeability, thrombosis, and organ dysfunction predominate.

Leukocyte infection

- *E. Chaffeensis* predominantly infects monocytes.
- *A. Phagocytophilum* predominantly infects neutrophils.

A practical recognition framework

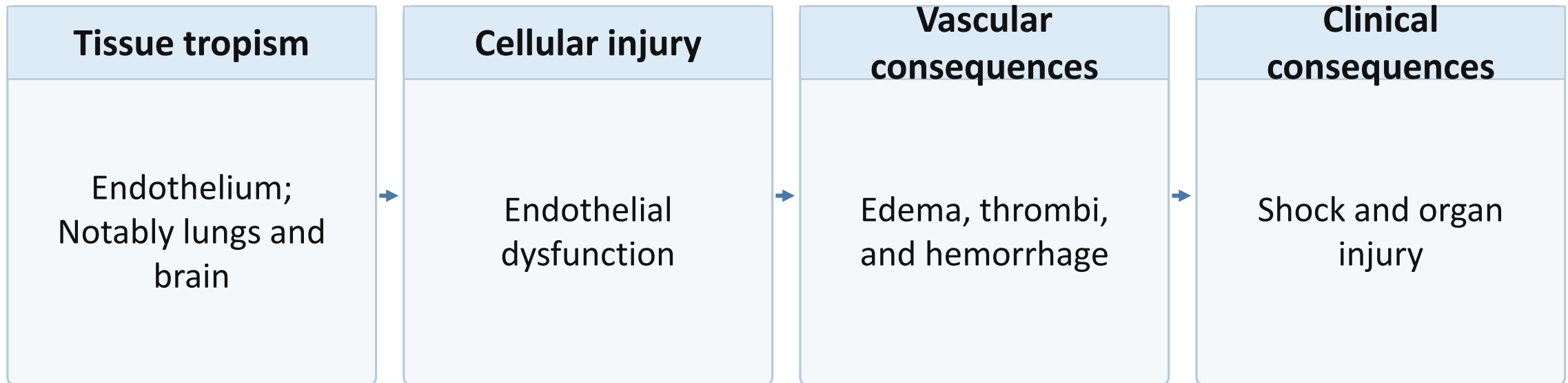
Exposure	Distribution	Compartment
Louse, mite, or particular tick	Characteristic rash or eschar	Vessels versus circulating leukocytes

Mechanism + vector + morphology provide a stronger classification than fever alone.

Four clinical syndromes, four distinguishing clues

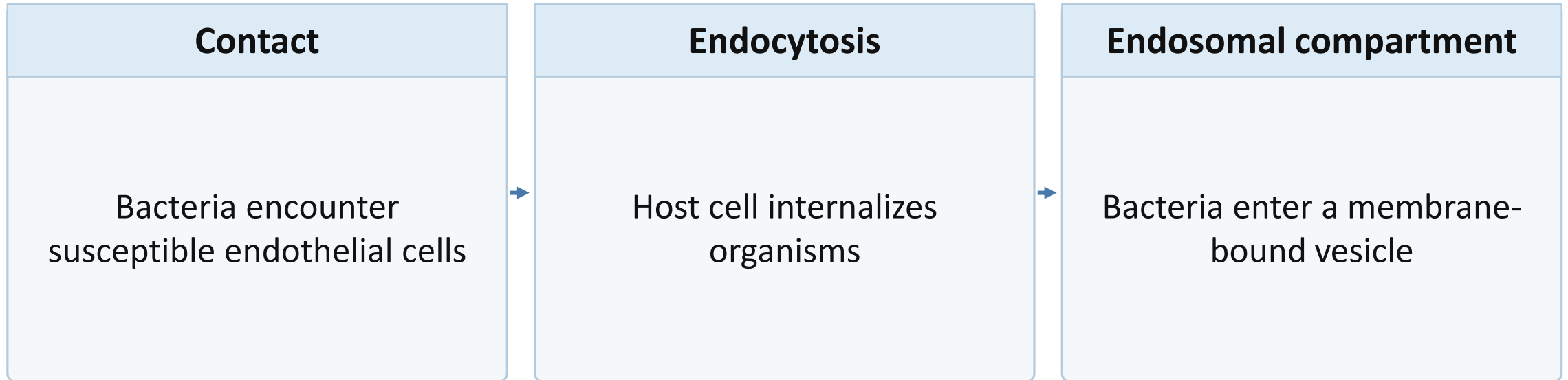
Disease	Characteristic clue	Primary pathology clue
Epidemic typhus	Louse exposure; rash usually spares palms/soles	Endothelial swelling; mononuclear cuffs
Scrub typhus	Mite exposure; possible eschar	Lymphadenopathy; less vascular necrosis
RMSF	Tick exposure; palms/soles may be involved	Small-vessel necrosis and fibrin
Ehrlichiosis / anaplasmosis	Tick exposure; systemic febrile illness	Morulae within leukocytes

Rickettsial severity begins in endothelial cells



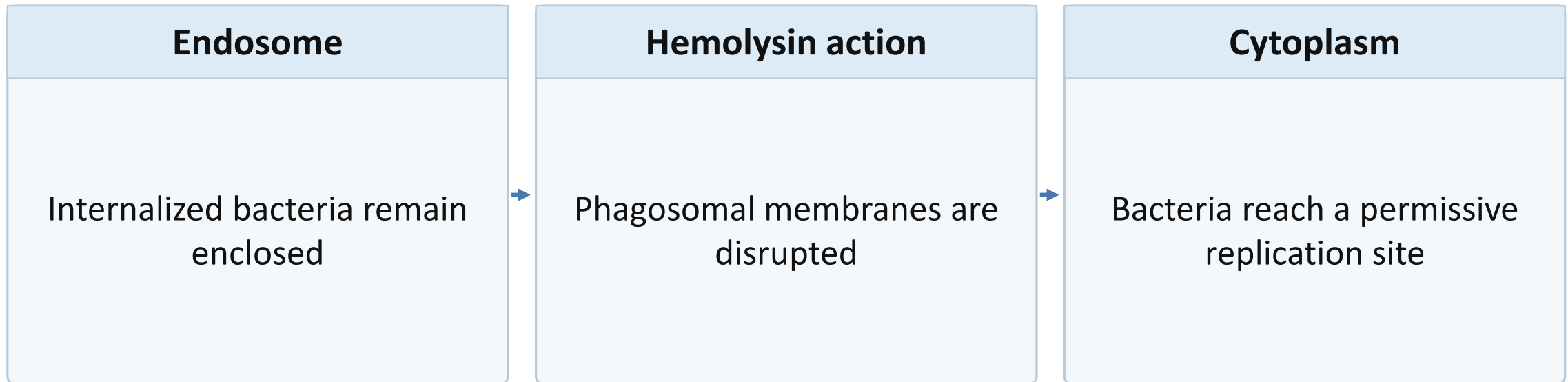
The endothelial cell is the central pathophysiologic target.

Cell entry starts by endocytosis



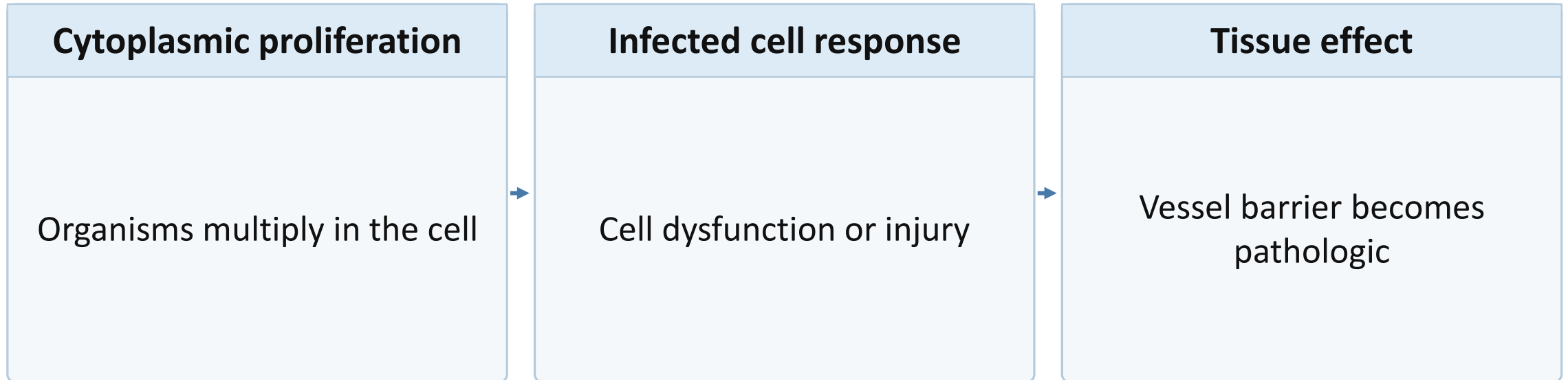
Cell entry is distinct from the next step: Endosomal escape.

Hemolysins enable escape from the endosome



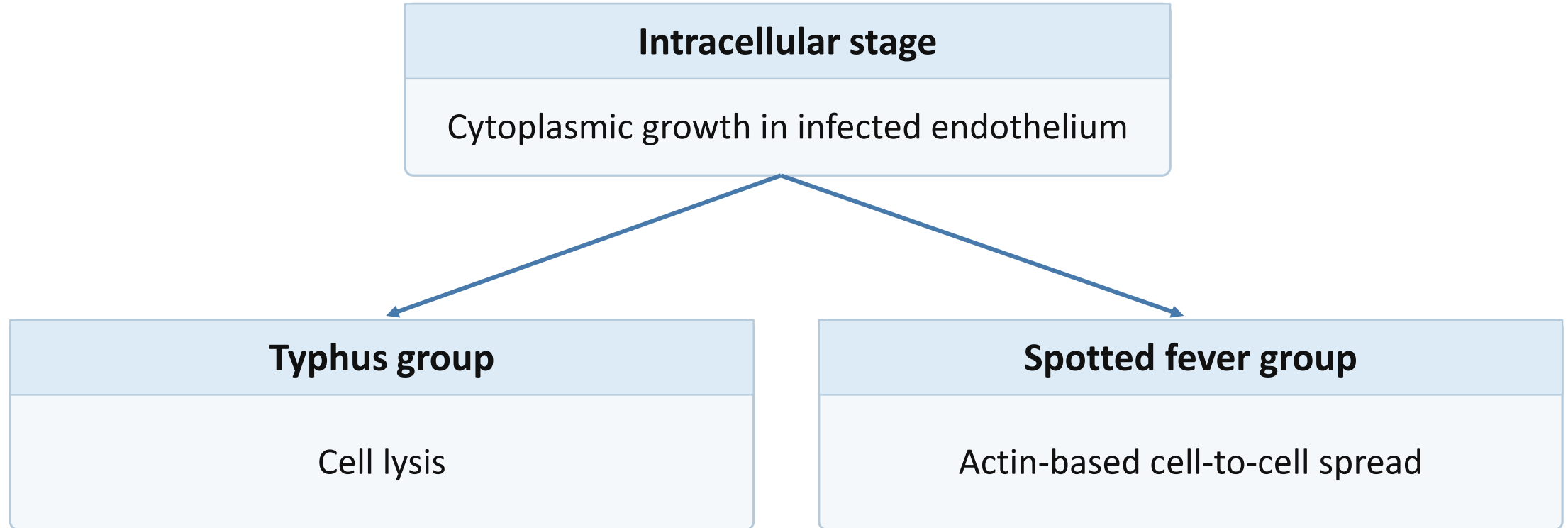
Escape into cytoplasm is a key rickettsial survival mechanism.

Intracytoplasmic proliferation changes endothelial integrity



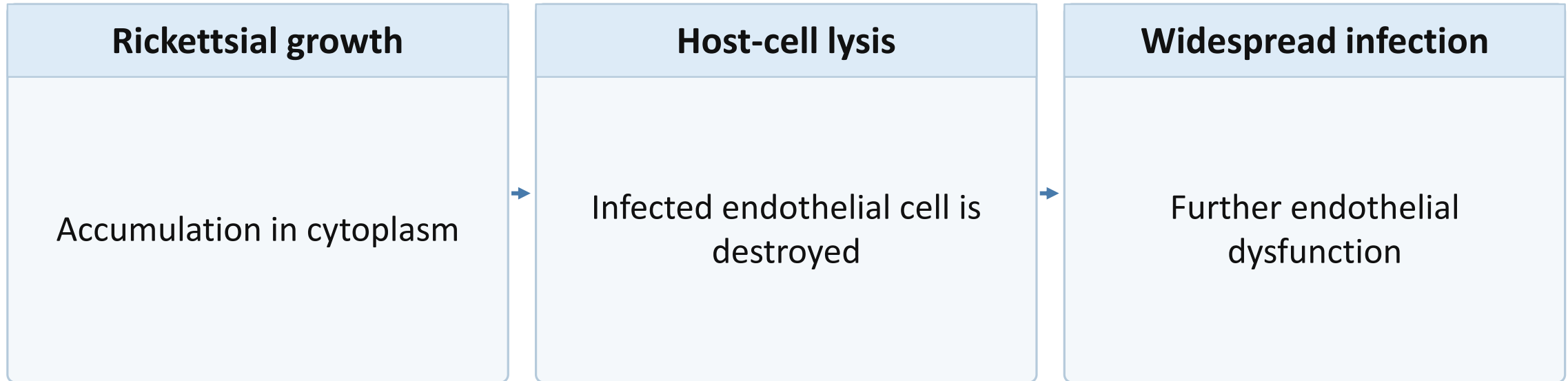
A microscopic intracellular event can cause distributed vascular disease.

Two distinct exits from infected cells



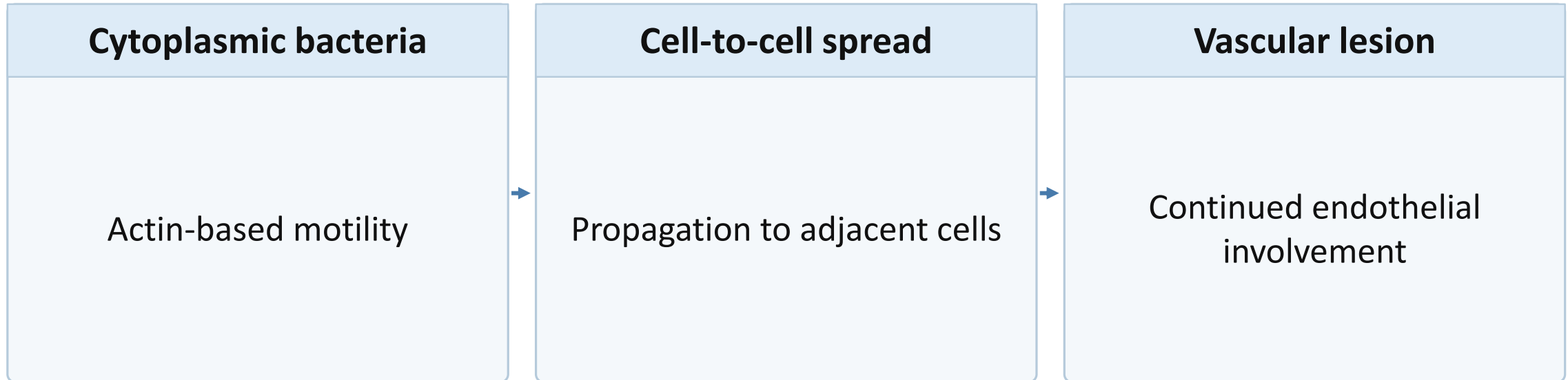
The source explicitly distinguishes these two mechanisms of propagation.

Typhus-group propagation involves cellular lysis



Cell lysis explains one mechanism for vascular barrier injury.

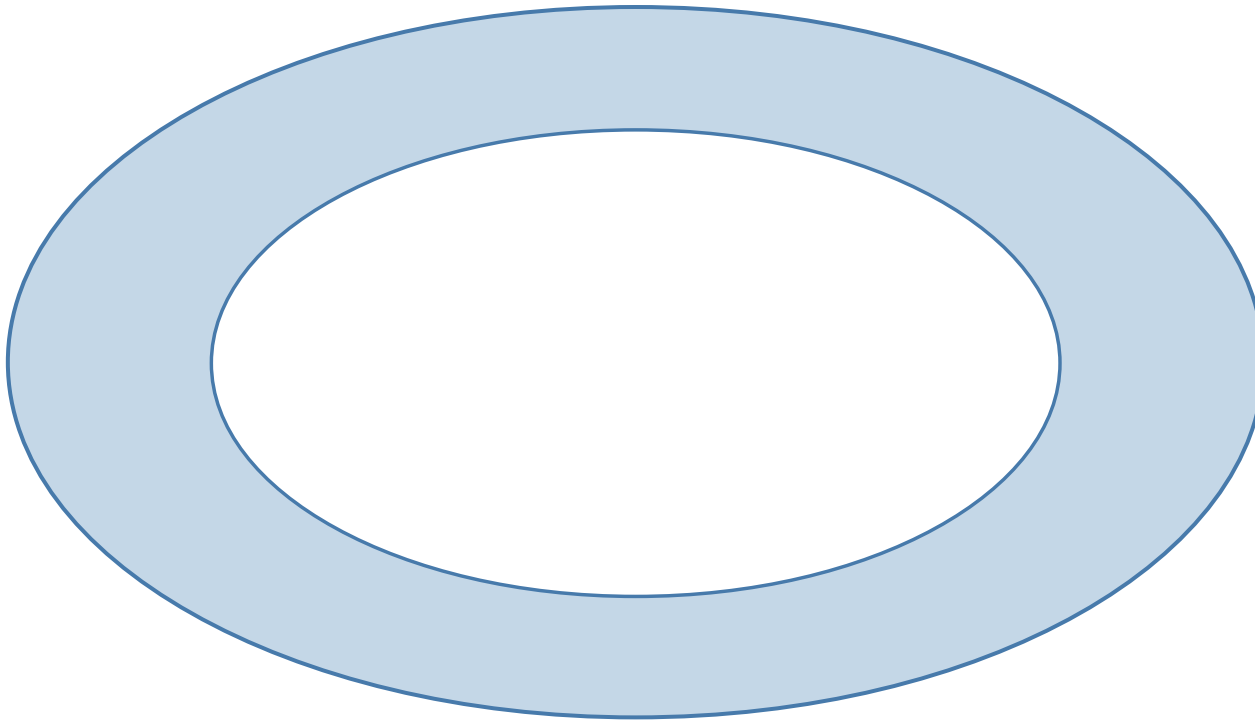
Spotted-fever rickettsiae use actin-based motility



The spotted-fever group can spread without relying solely on host-cell lysis.

Endothelial swelling narrows the vascular lumen

Small-vessel cross-section • original schematic



Narrowed lumen

- Capillaries, arterioles, and venules are affected.
- Swollen endothelium reduces the available vessel lumen.
- Impaired microvascular passage contributes to tissue injury.

Increased permeability produces interstitial edema

Endothelial dysfunction

Injured vascular barrier



Fluid movement

Edema develops in peripheral tissues



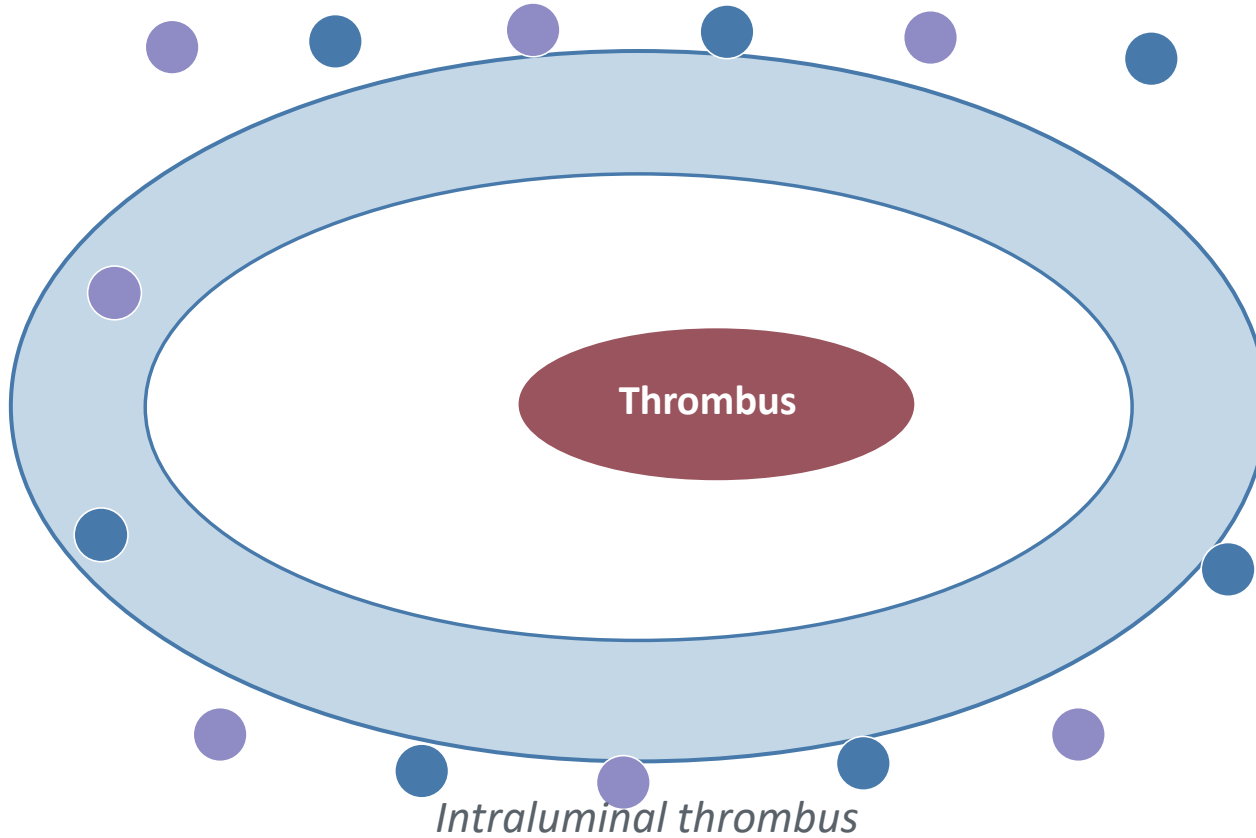
Pulmonary involvement

Pulmonary edema may impair breathing

The same small-vessel lesion has different effects in different organs.

Vascular thrombosis intensifies ischemic injury

Small-vessel cross-section · original schematic



- Vascular lumens can become thrombosed.
- Thrombi reduce local blood flow.
- Severe focal ischemia may cause tissue necrosis.

Severe endothelial injury may produce DIC

Disseminated endothelial damage

Systemic vascular dysfunction



Coagulation disturbance

Disseminated intravascular coagulation



Clinical threat

Shock and multiorgan involvement

DIC is a potential consequence, not a universal presentation.

Renal injury and shock are vascular consequences

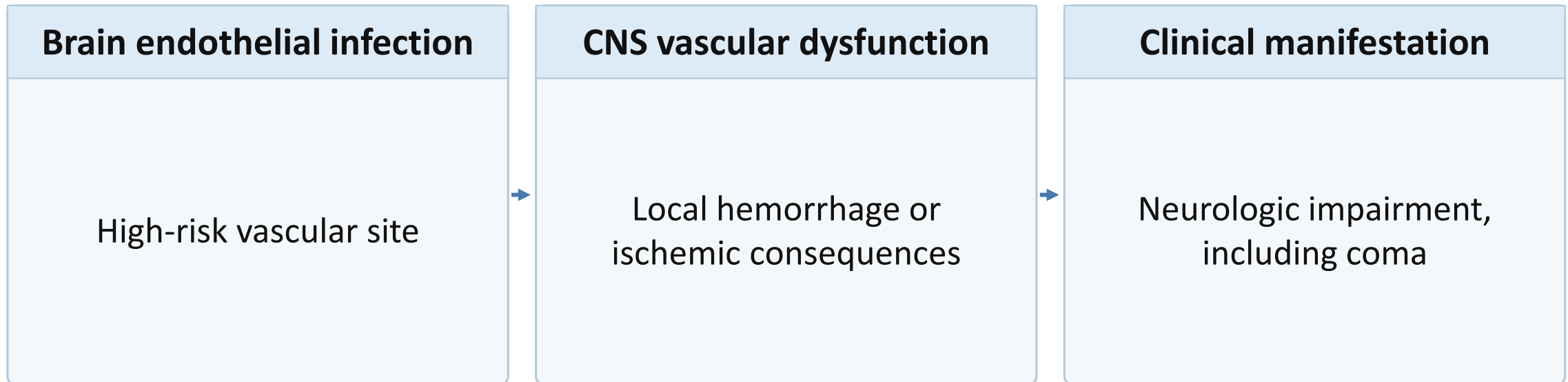
Renal effects

- Widespread endothelial dysfunction can compromise renal function.
- Renal failure is among the severe complications.

Systemic hemodynamics

- Vascular dysfunction may contribute to shock.
- Concomitant pulmonary edema and DIC can worsen severity.

CNS manifestations reflect brain vascular tropism

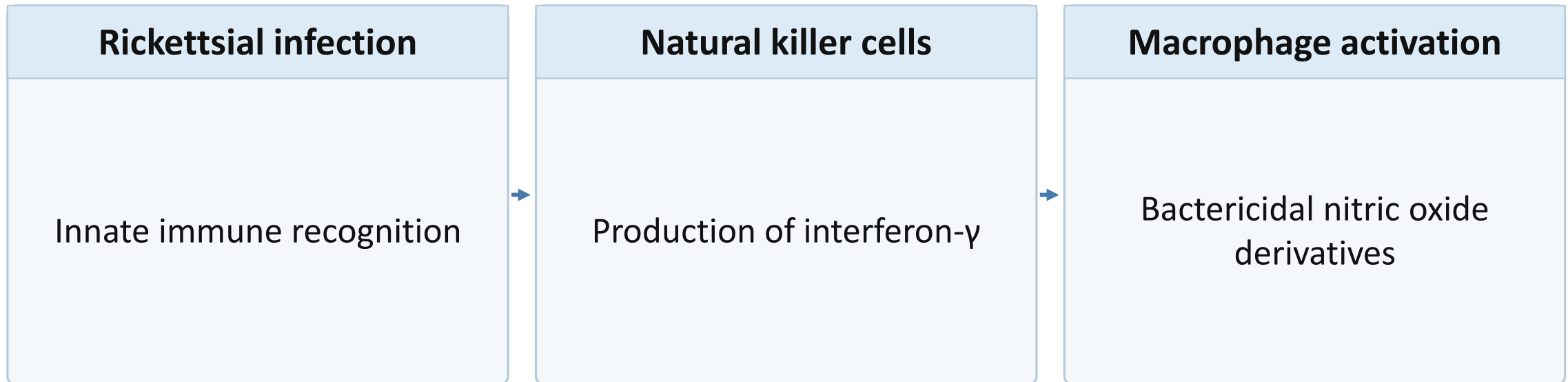


CNS disease is linked to vascular pathogenesis, not just systemic fever.

Endothelial lesions connect skin and organ manifestations

Organ / tissue	Mechanistic lesion	Pathologic / clinical result
Skin	Vascular leakage and thrombosis	Petechiae, necrotic lesions
Brain	Vascular injury; focal inflammation	Microglial nodules or microinfarcts
Lungs	Vascular dysfunction	Pulmonary edema, respiratory compromise
Kidneys	Microvascular injury	Renal dysfunction / failure

Innate defense includes NK-cell interferon- γ



NK-cell signaling promotes an antimicrobial macrophage response.

Macrophage nitric oxide contributes to bacterial killing

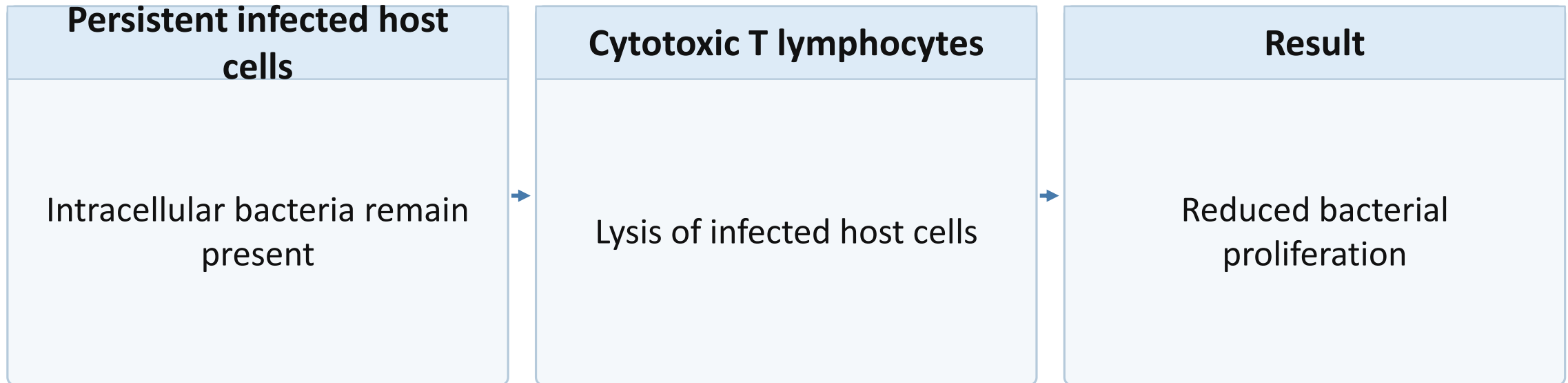
Signal

- NK cells produce IFN- γ during the innate response.
- IFN- γ stimulates macrophages.

Effector

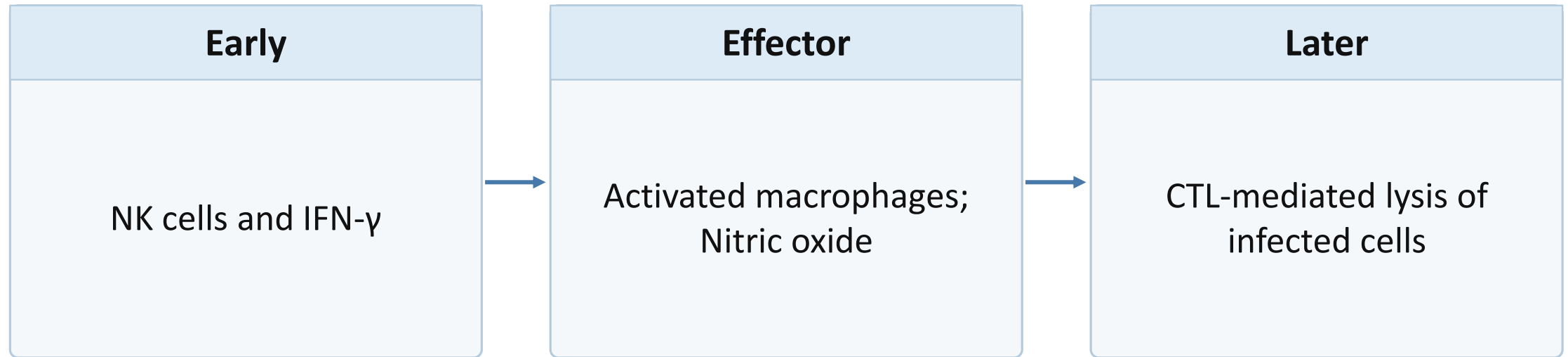
- Macrophages generate bactericidal nitric oxide derivatives.
- This limits survival of intracellular organisms.

Cytotoxic T lymphocytes act later



Cell-mediated immunity is central to defense against intracellular pathogens.

The host response develops in phases



A conceptual sequence from the textbook—not a quantitative timeline.

Vascular injury is the unifying morphologic principle

Barrier injury

Edema and hemorrhage

Luminal injury

Thrombosis and ischemia

Inflammatory response

Perivascular mononuclear
infiltrates

Different organisms vary in severity and pattern of these features.

Epidemic typhus is caused by *R. Prowazekii*

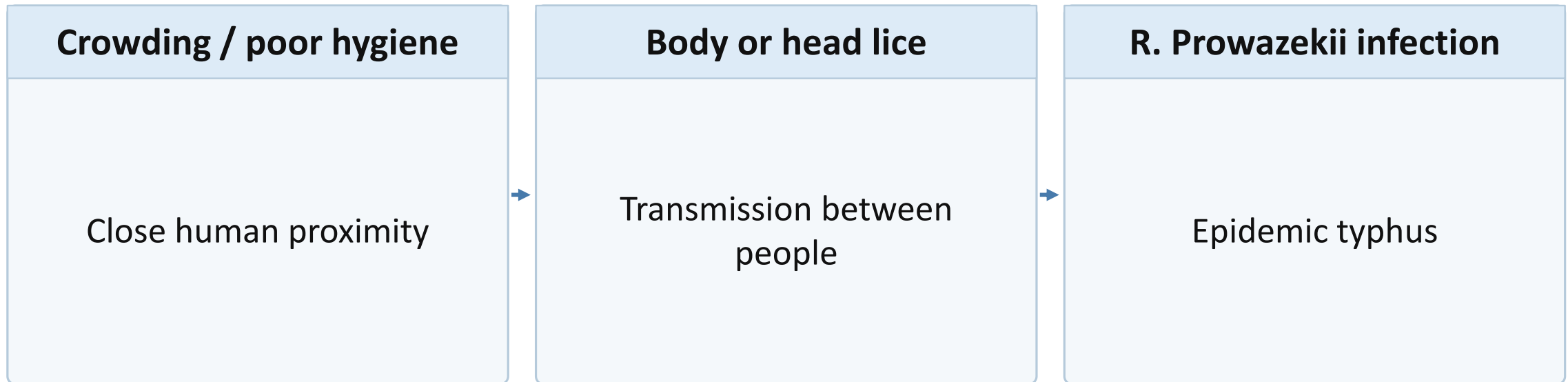
Cause and transmission

- *Rickettsia prowazekii*
- Body and head lice mediate transmission.

Exposure setting

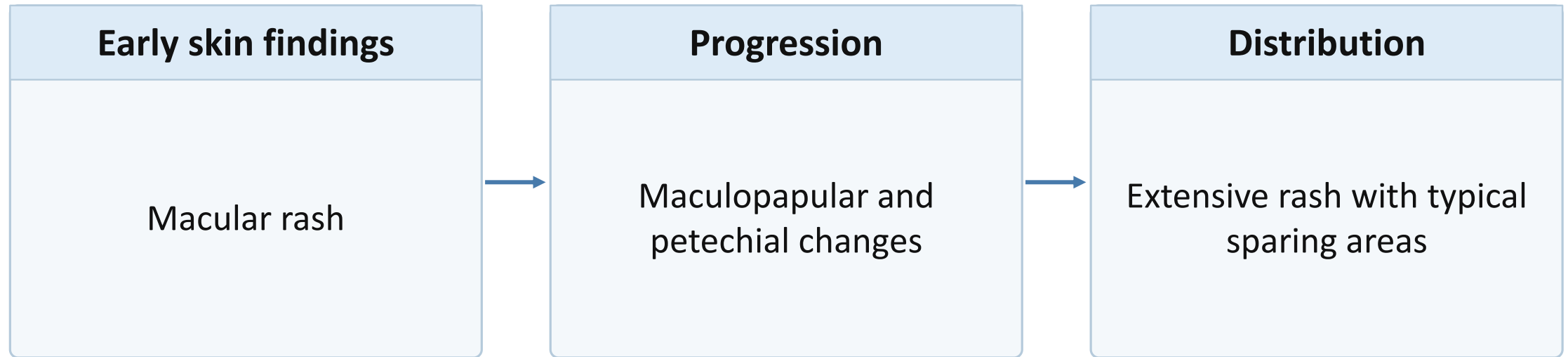
- Crowding and inadequate hygiene
- War and poverty facilitate outbreaks.

The epidemiology reflects close-contact settings



The social environment modifies vector exposure.

Epidemic typhus rash changes with time



The evolution of rash reflects ongoing vascular injury.

Typhus typically spares face, palms, and soles

Usually involved	Typically spared	Interpretation
Most of the body	Face	Distribution supports epidemic typhus
Trunk and limbs	Palms and soles	Compare with RMSF
Skin microvessels	—	Rash is a vascular manifestation

Mild typhus may show little gross pathology

- Mild cases may have a skin rash as the main visible finding.
- Small hemorrhages result from vascular lesions.
- Gross abnormalities need not reflect the full microscopic vascular disease.

Severe typhus can cause peripheral gangrene

Ischemic trigger	Sites described	Other sites
Small-vessel thrombosis	Fingertips, nose and ear lobules	Scrotum, penis, and vulva

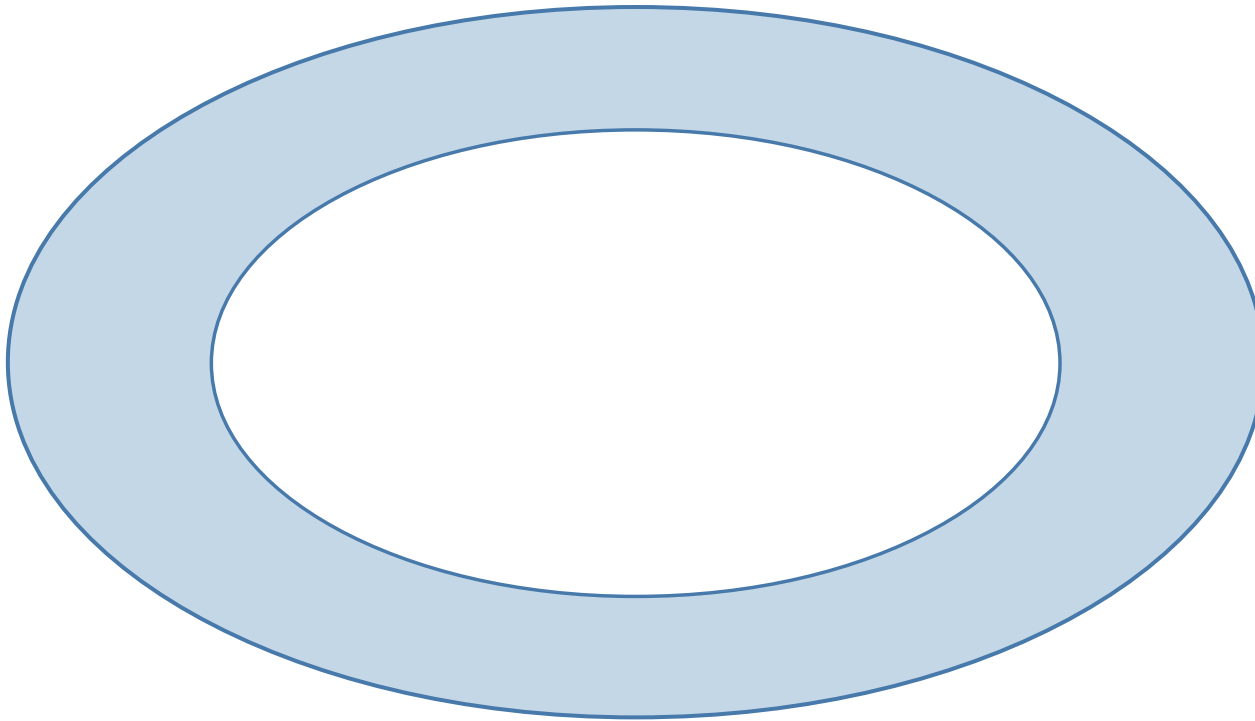
Cutaneous necrosis occurs in severe disease, not in every patient.

Internal hemorrhage reflects systemic vasculopathy

Sites reported in severe typhus	Observed lesion
Brain and heart muscle	Irregular ecchymotic hemorrhages
Testes and serosal membranes	Irregular ecchymotic hemorrhages
Lungs and kidneys	Irregular ecchymotic hemorrhages

Typhus microangiopathy involves small vessels

Small-vessel cross-section • original schematic

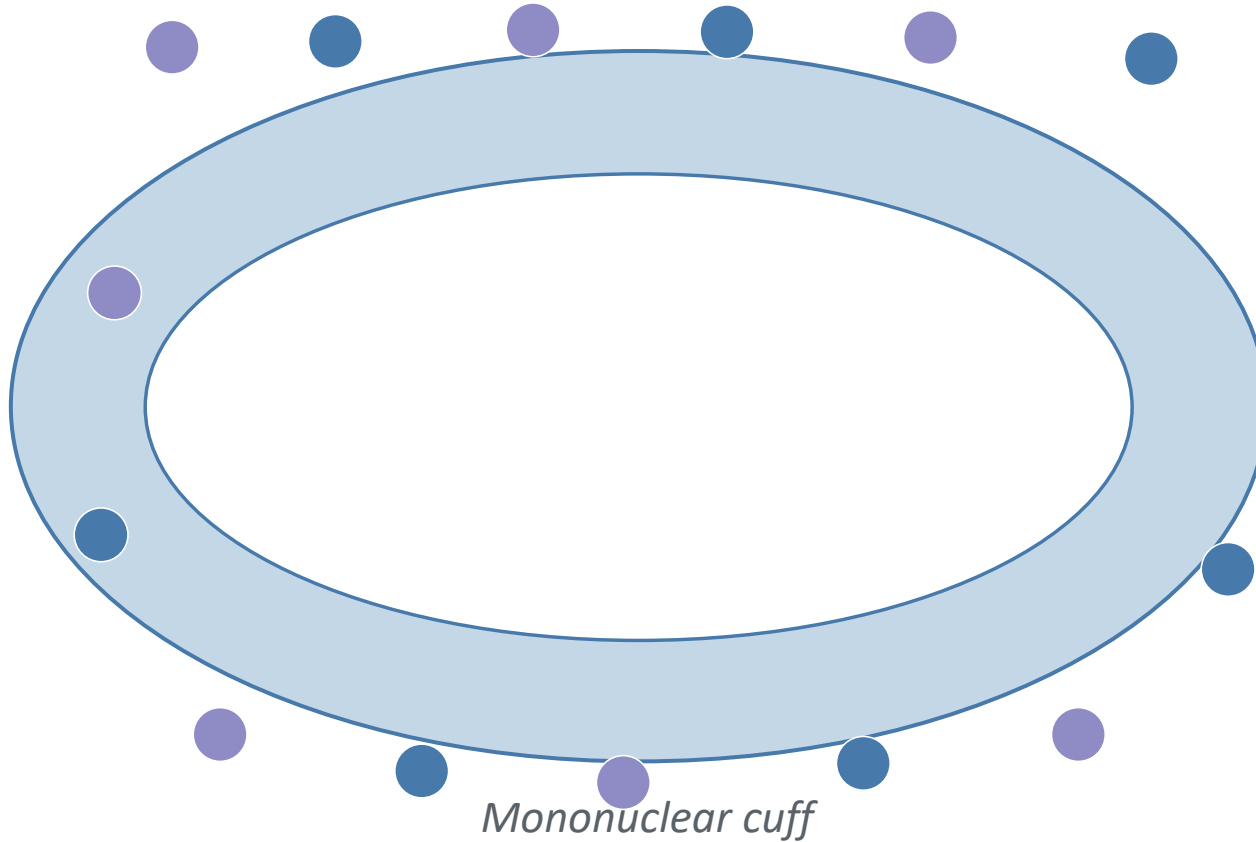


Narrowed lumen

- Capillaries, arterioles, and venules are affected.
- Endothelial swelling may narrow vascular lumens.
- Hemorrhage and focal inflammation occur across organs.

Mononuclear perivascular cuffs are characteristic

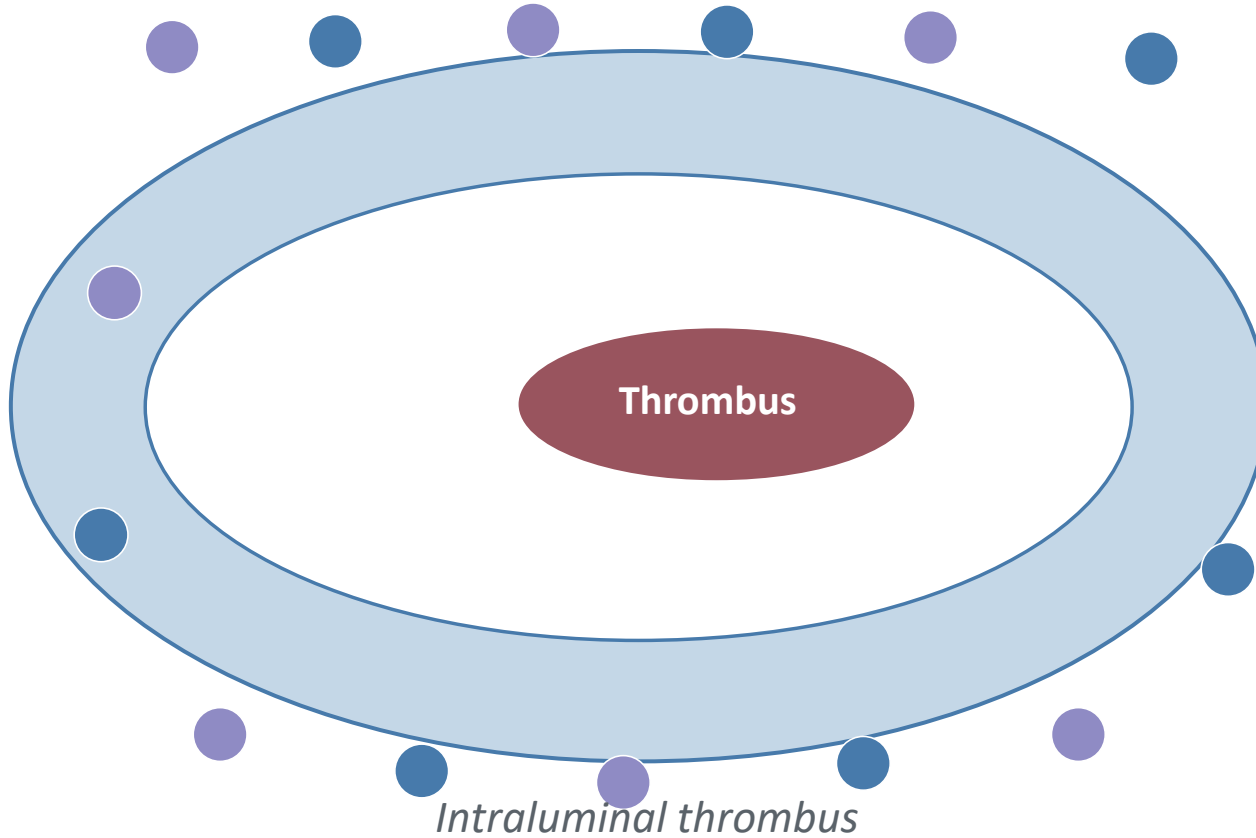
Small-vessel cross-section • original schematic



- Mononuclear inflammatory cells encircle affected small vessels.
- The infiltrate surrounds an abnormal endothelial-lined lumen.
- This is a histologic pattern rather than an organism-specific stain.

Vascular thromboses in typhus are variable

Small-vessel cross-section · original schematic



- Vessel lumens may contain thrombi.
- Only a minority develop thrombosis-associated ischemic necrosis.
- Vessel-wall necrosis is unusual compared with RMSF.

Typhus nodules are focal inflammatory lesions of the brain

Microglia

Focal microglial proliferation

T lymphocytes

Part of the mixed cellular
infiltrate

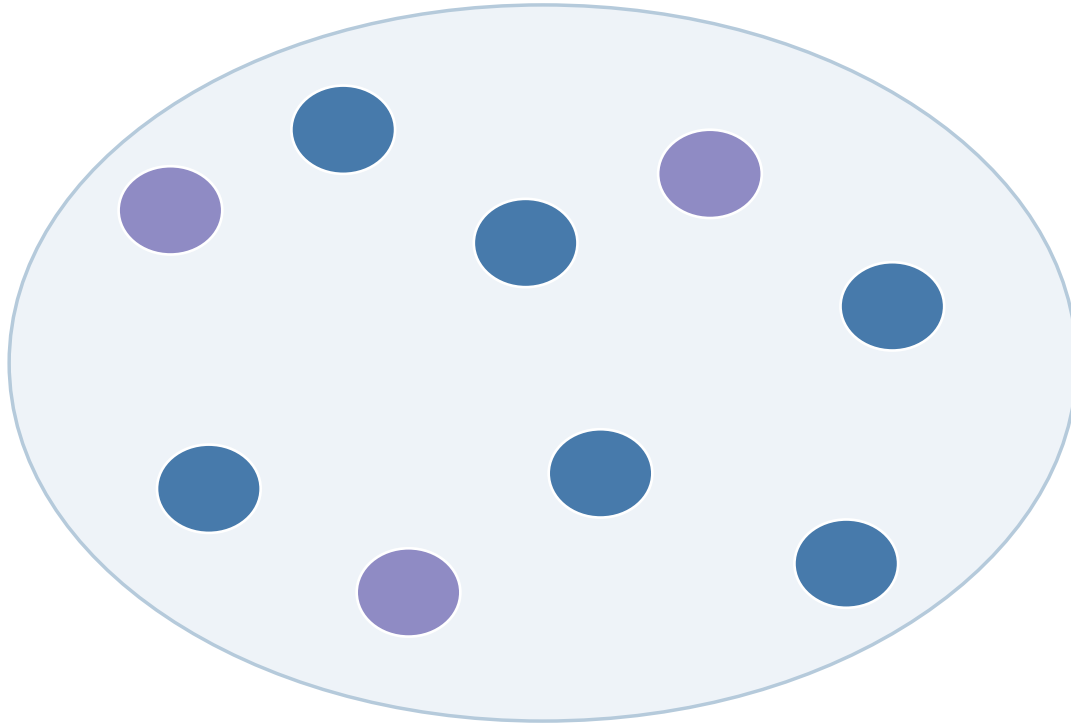
Macrophages

Coexist with the T-cell
infiltrate

The combination forms the characteristic typhus nodule.

Typhus nodule: Constituent cells

Original conceptual schematic · not a microscopy image



Microglia + T cells + macrophages

- Focal microglial proliferation forms the central feature.
- Mixed T lymphocytes and macrophages accompany the microglia.
- The drawing is a compartmental schematic, not a brain photomicrograph.

Typhus: Correlate skin, vessel, and brain

Level	Finding	Why it matters
Clinical	Evolving widespread rash	Vascular injury at the skin
Microscopic vessel	Swelling and mononuclear cuffs	Small-vessel pathology
Severe disease	Thrombosis and ischemic necrosis	Threatened tissue perfusion
Brain	Typhus nodules	Characteristic neuroinflammatory lesion

Scrub typhus is an Orientia infection

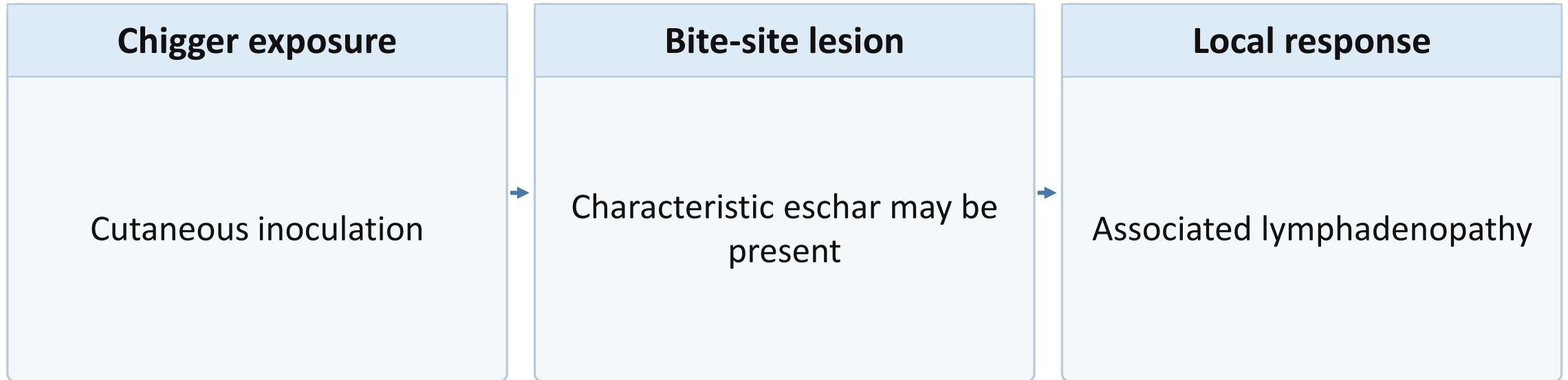
Organism and vector

- *Orientia tsutsugamushi*
- Transmitted by chiggers (mites).

Source-described geography

- Rural Asia and Australia
- Reported emergence in South Korea, Chile, and parts of China

A chigger bite can produce an eschar



The eschar is helpful when present, but not obligatory.

Scrub typhus often presents as a systemic febrile illness

- Usual symptoms are fever, headache, and myalgia.
- Cough may accompany systemic symptoms.
- A characteristic eschar and regional lymphadenopathy are possible clues.
- The rash may be transient or absent.

Scrub typhus differs morphologically from severe typhus

Scrub typhus

- Vascular necrosis or thrombosis is rare.
- Inflammatory lymphadenopathy may be prominent.
- Rash is often transient or absent.

Epidemic typhus

- Small-vessel changes and hemorrhage are prominent.
- Thrombosis may produce ischemic necrosis.
- Widespread evolving rash is described.

RMSF is a tick-borne spotted fever

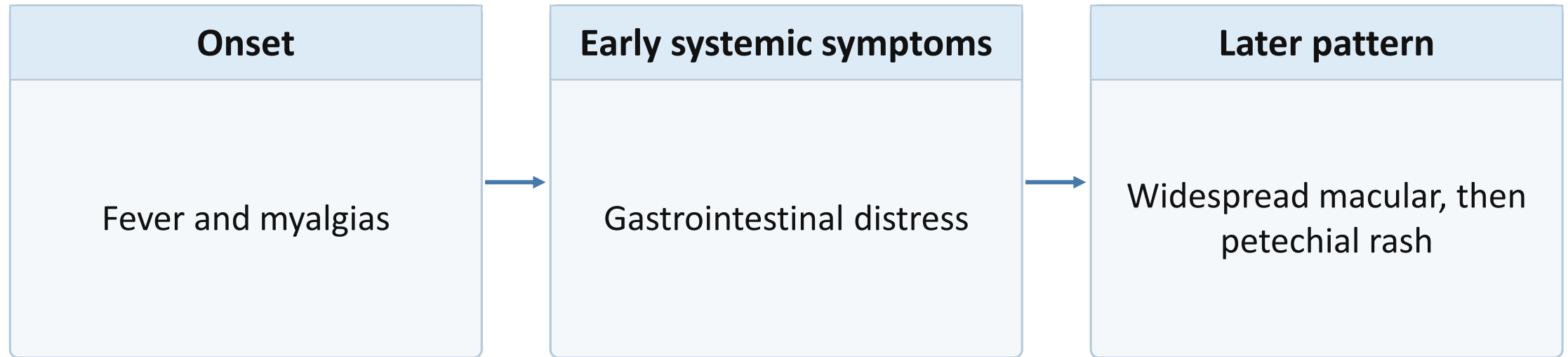
Agent and transmission

- *Rickettsia rickettsii*
- Dog ticks transmit infection to humans.

Distribution described

- Southeastern and south-central United States are emphasized.
- Also occurs elsewhere in the Americas.

Early RMSF may be clinically nonspecific



Do not expect the characteristic rash at the first symptomatic moment.

Palms and soles help distinguish RMSF rash

Rocky Mountain spotted fever

- Macular rash progresses to petechiae.
- Palms and soles can be involved.

Epidemic typhus

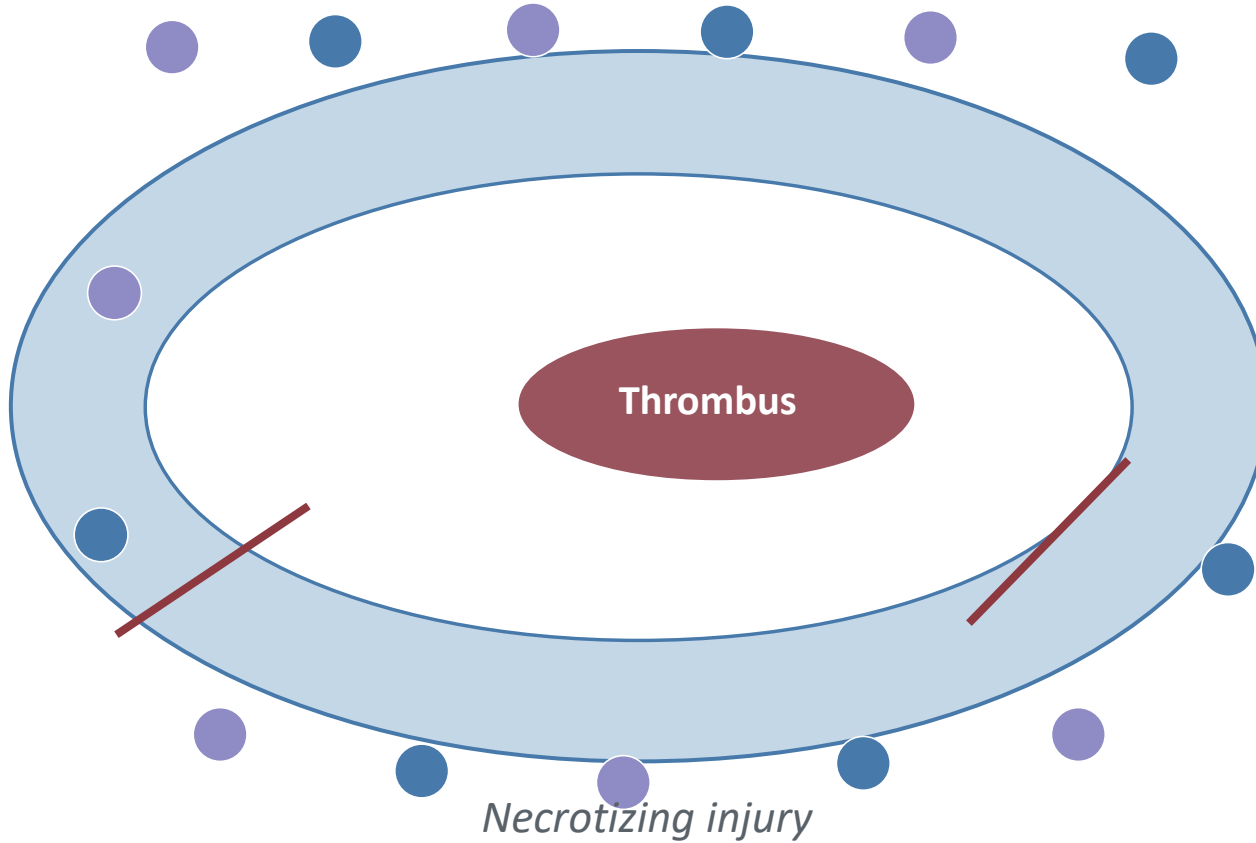
- Macular eruption also becomes petechial.
- Palms and soles are typically spared.

Eschar is uncommon in RMSF

- The infection is transmitted by tick bite.
- An eschar at the inoculation site is uncommon with RMSF.
- An eschar is more characteristic of scrub typhus when present.
- The rash distribution and vascular pathology are more useful comparative clues.

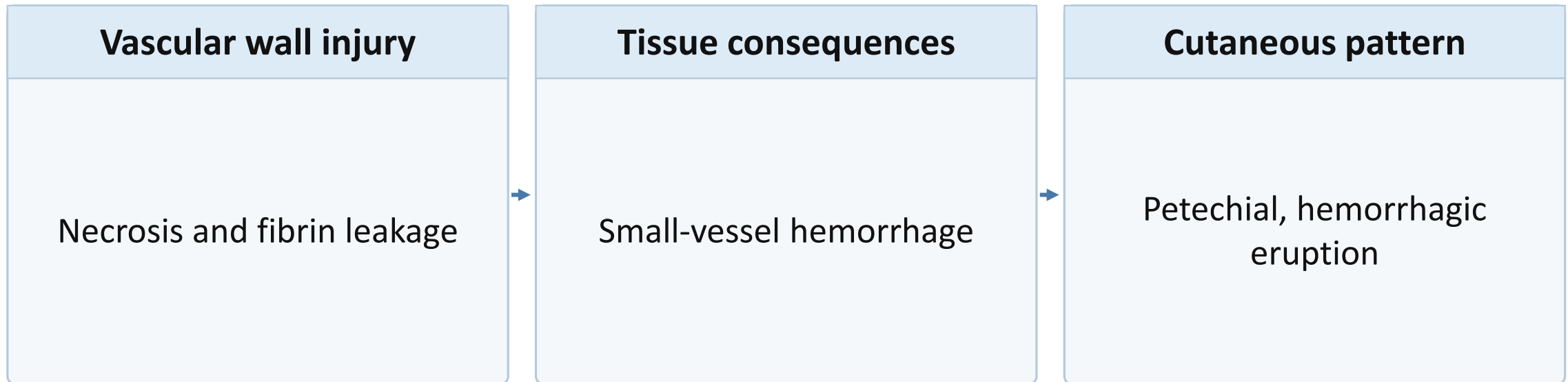
RMSF shows more destructive vessel-wall lesions

Small-vessel cross-section · original schematic



- Small vessels may undergo acute necrosis.
- Fibrin can extravasate from injured vessels.
- Thrombosis may involve arterioles and other small vessels.

RMSF vasculitis explains the hemorrhagic rash



The rash is an outward manifestation of systemic vascular injury.

Severe RMSF may produce distal skin necrosis

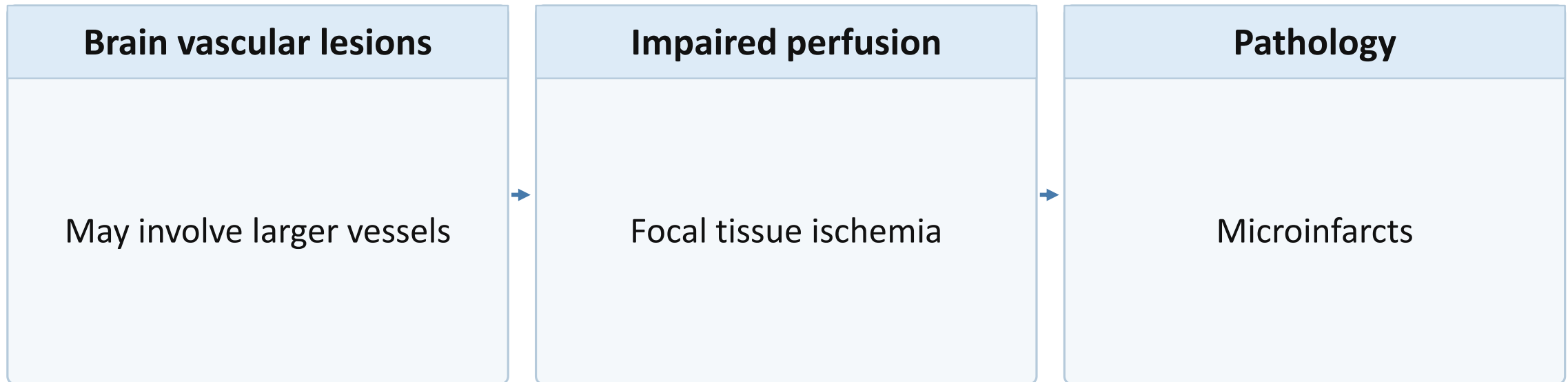
Digits	Prominent sites	Other described site
Fingers and toes	Elbows and ears	Scrotum

These foci reflect severe vascular compromise.

RMSF affects multiple organ systems

Tissue	Source-described pathology / consequence
Brain	Perivascular inflammation; microinfarcts
Skeletal muscle	Perivascular inflammatory response
Lungs and kidneys	Perivascular inflammatory response
Testes and heart muscle	Perivascular inflammatory response

Brain vasculopathy can produce microinfarcts



Brain lesions in RMSF are not limited to perivascular inflammatory cuffs.

Severe pulmonary edema is a major lethal pathway

Endothelial dysfunction in pulmonary vessels

Microvascular barrier failure



Noncardiogenic pulmonary edema

Acute respiratory distress syndrome



Severe disease

Major cause of death described in RMSF

The source identifies pulmonary failure as a principal fatal complication.

Typhus and RMSF: Pathologic discriminators

Finding	Epidemic typhus	RMSF
Endothelial swelling	Prominent	Possible in vascular disease
Vessel-wall necrosis	Unusual	May occur in affected vessels
Vascular thrombosis	Sometimes	Occasionally
Brain lesion	Typhus nodules	Vascular lesions with microinfarcts
Skin distribution	Palms/soles spared	Palms/soles may be involved

Ehrlichiosis and anaplasmosis target leukocytes

Ehrlichiosis

- Main organism: *Ehrlichia chaffeensis*
- Predominant infected leukocyte: Monocyte

Anaplasmosis

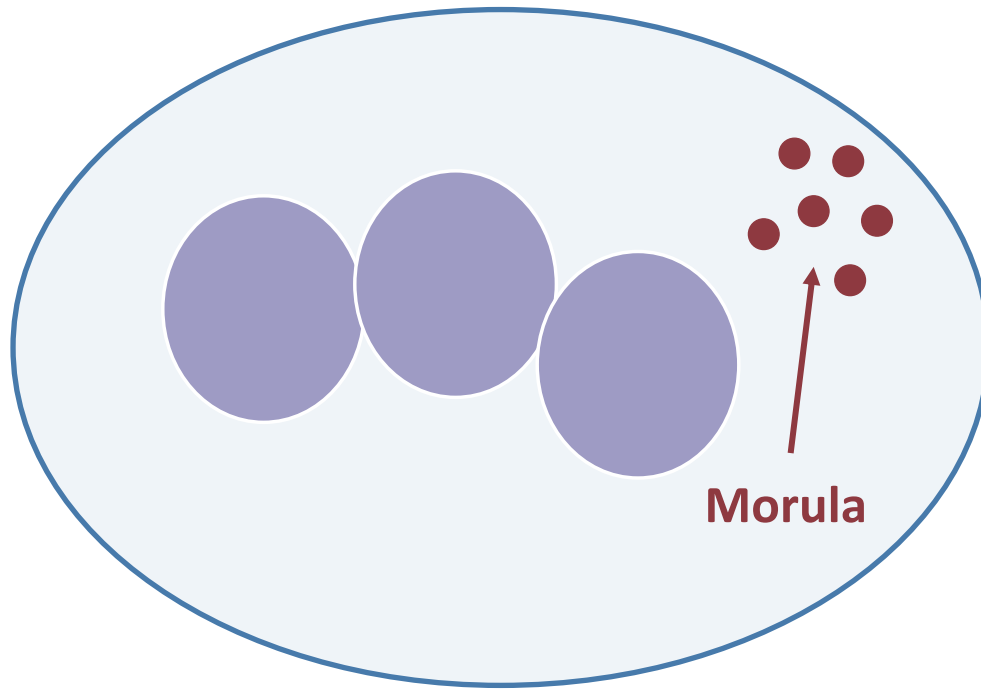
- Organism: *Anaplasma phagocytophilum*
- Predominant infected leukocyte: Neutrophil

Two tick associations, two cell targets

Feature	Ehrlichiosis	Anaplasmosis
Vector	Lone star tick	Deer tick
Organism	<i>E. chaffeensis</i>	<i>A. phagocytophilum</i>
Cell tropism	Monocyte	Neutrophil
Characteristic inclusion	Morulae	Morulae

Morulae are bacterial inclusions in leukocytes

Original conceptual schematic · not a microscopy image



Neutrophil (anaplasmosis model)

- Morulae are cytoplasmic clusters composed of masses of bacteria.
- Their aggregates may have a mulberry-like appearance.
- They may be seen in leukocytes in ehrlichiosis and anaplasmosis.

Ehrlichiosis and anaplasmosis often begin abruptly

- An abrupt onset of fever is typical.
- Headache and malaise commonly accompany the fever.
- Both diseases may have similar presenting symptoms.
- The infected leukocyte type provides an etiologic distinction.

Rash is variable in ehrlichial and anaplasma disease

Ehrlichiosis

- Rash occurs in approximately 40% of E. Chaffeensis infections.
- Macular, maculopapular, or petechial morphology may occur.

Both infections

- Rash is nonspecific when present.
- Absence of rash does not negate the source-described febrile syndrome.

Severe ehrlichial or anaplasmal illness can escalate

Abrupt febrile illness

Headache and malaise



Severe systemic disease

Respiratory insufficiency



Organ dysfunction

Renal failure and shock

These are possible complications, not automatic consequences.

Leukocyte morulae do not imply vascular-wall necrosis

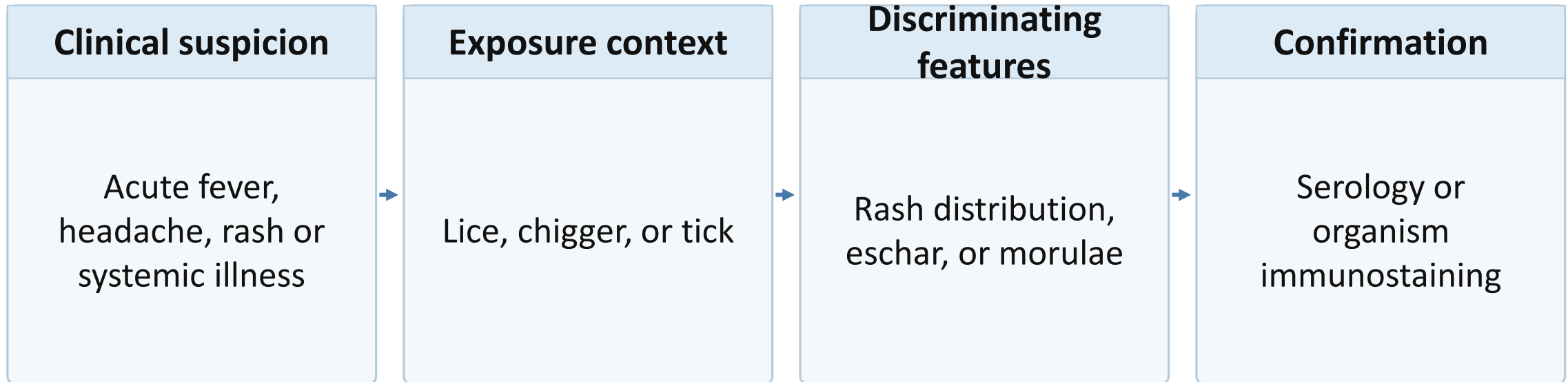
Ehrlichia / Anaplasma

- Characteristic inclusion: Morulae in leukocytes.
- Cell tropism: Monocytes or neutrophils.

Rickettsial typhus / spotted fever

- Core pathogenetic lesion: Endothelial infection.
- Cellular injury leads to systemic vasculopathy.

Start diagnosis with the clinical syndrome



Clinical diagnosis with confirmatory serology or immunostaining for rickettsial diseases.

Histologic patterns should be interpreted in context

Observation	Interpretation supported by Robbins
Mononuclear perivascular cuffs	Typical typhus microvascular response
Vascular necrosis with fibrin leakage	Supports RMSF-type vasculitis
Focal microglial nodule	Characteristic brain lesion of typhus
Cytoplasmic leukocyte morulae	Supports ehrlichial or anaplasma infection

Gram staining is not a reliable exclusion tool

What it can show

- The group has gram-negative bacterial structure.
- Routine Gram staining may reveal little organism detail.

What else contributes

- Epidemiologic and clinical pattern
- Rickettsial serology or organism immunostaining

A four-syndrome side-by-side diagnosis map

Illness	Vector	Rash clue	Tissue / cell clue
Epidemic typhus	Lice	Spared palms/soles	Perivascular cuff; typhus nodule
Scrub typhus	Chigger	Often absent or transient	Eschar; lymphadenopathy
RMSF	Tick	May involve palms/soles	Necrotizing small-vessel injury
Ehrlichiosis / anaplasmosis	Tick	Nonspecific / variable	Leukocyte morulae

Case application: Fever following louse exposure

Illustrative teaching scenario

A patient from a crowded setting with poor hygiene has an evolving macular-to-petechial rash. Palms and soles are spared. Biopsy shows swollen small-vessel endothelium with mononuclear cuffs.

Which infection best fits, and what is the major pathologic target?

Clues to weigh

- Louse-associated setting
- Rash distribution
- Small-vessel endothelial lesion

Case interpretation: Epidemic typhus

Epidemic typhus — *Rickettsia prowazekii*

- Louse transmission is a defining exposure clue.
- Palms and soles are typically spared.
- Endothelial infection explains the perivascular changes and rash.

Severe cases can progress to hemorrhage, thrombosis, and peripheral necrosis.

Case application: Rash reaches the palms and soles

Illustrative teaching scenario

A patient develops fever, severe myalgias, gastrointestinal symptoms, and then a petechial eruption involving palms and soles after tick exposure.

Which illness and which tissue lesion should be anticipated?

Clues to weigh

- Tick-related systemic disease
- Progressing petechial rash
- Palmar and plantar involvement

Case interpretation: Rocky Mountain spotted fever

Rocky Mountain spotted fever — *Rickettsia rickettsii*

- A tick-associated illness precedes an evolving petechial rash.
- Palmar and plantar involvement is a characteristic clinical clue.
- Small-vessel necrosis and fibrin extravasation distinguish the pathologic pattern.

Major severe complication: Noncardiogenic pulmonary edema with ARDS.

Case application: Inclusions in granulocytes

Illustrative teaching scenario

A patient presents with abrupt fever, headache, and malaise following a deer-tick exposure. Blood examination shows clusters of bacterial inclusions in neutrophil cytoplasm.

Identify the likely agent and name the cytoplasmic structure.

Clues to weigh

- Deer-tick exposure
- Neutrophil tropism
- Cytoplasmic clusters

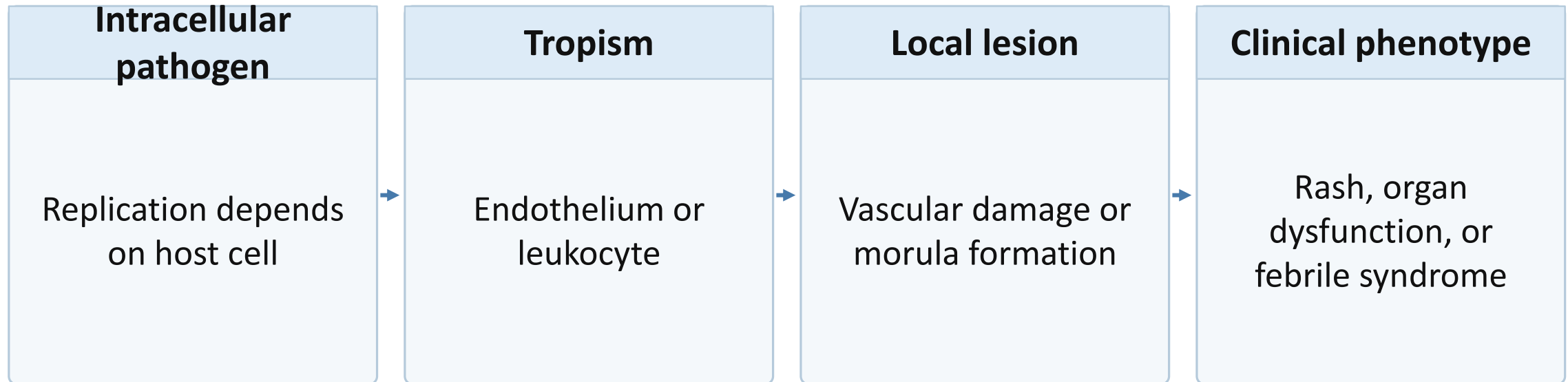
Case interpretation: Anaplasmosis

Anaplasmosis — *Anaplasma phagocytophilum*

- Deer ticks are the source-described vector.
- *A. Phagocytophilum* predominantly infects neutrophils.
- The bacterial cytoplasmic inclusions are morulae.

Differentiate *E. Chaffeensis* by its monocyte tropism and lone-star-tick association.

Pathogenesis synthesis: Cell compartment to organ injury



Anatomical cell tropism creates the diagnostic logic of the group.

Morphology synthesis: Recognize the discriminators

Typhus

Perivascular mononuclear cuffs; Brain nodules

RMSF

Necrotizing vascular lesions and fibrin leakage

Anaplasmosis / ehrlichiosis

Morulae within affected leukocytes

Scrub typhus additionally emphasizes eschar and regional lymphadenopathy.

Final clinicopathologic distinctions

- Endothelial tropism explains the vascular pathology of typhus and spotted fevers.
- Rash distribution differs: Palms and soles are typically spared in epidemic typhus but may be involved in RMSF.
- Scrub typhus may feature an eschar and prominent lymphadenopathy.
- Leukocyte morulae identify the distinctive cellular pattern of ehrlichiosis and anaplasmosis.

References

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 8, Infectious Diseases.
- Obligate Intracellular Bacterial Infections; Infections Caused by Other Intracellular Bacteria; relevant Pathogenesis and Morphology sections.
- Original textbook figures 8.40–8.42 were described in the supplied text but were not reproduced; diagrams in this lecture are newly authored schematics.