

Viral hemorrhagic fever

Vascular injury, hemorrhage, immune evasion and organ pathology

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Learning outcomes

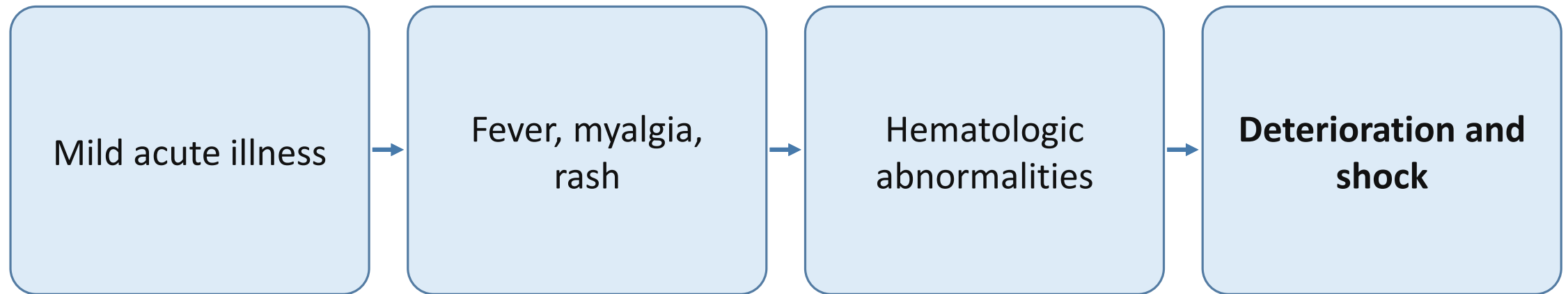
- Classify the principal viral groups and modes of exposure.
- Explain endothelial, cytokine-mediated and hemostatic injury.
- Relate Ebola immune evasion to multiorgan morphology.
- Differentiate the mechanism of severe dengue from filoviral disease.

A multisystem syndrome, not one virus

Vascular damage is the unifying lesion.

- The clinical syndrome may culminate in widespread hemorrhage and shock.
- Different viral groups can produce overlapping manifestations.
- Etiology and severity vary across infections.

Clinical disease spans a broad severity range



Potential clinical spectrum—not an inevitable sequence for every patient

Hemorrhage is not required at presentation

Early / mild spectrum

- Fever and headache
- Myalgia and rash
- Neutropenia and thrombocytopenia

Severe spectrum

- Hemorrhagic manifestations
- Hemodynamic deterioration
- Shock and multiorgan injury

The implicated viruses are enveloped RNA viruses

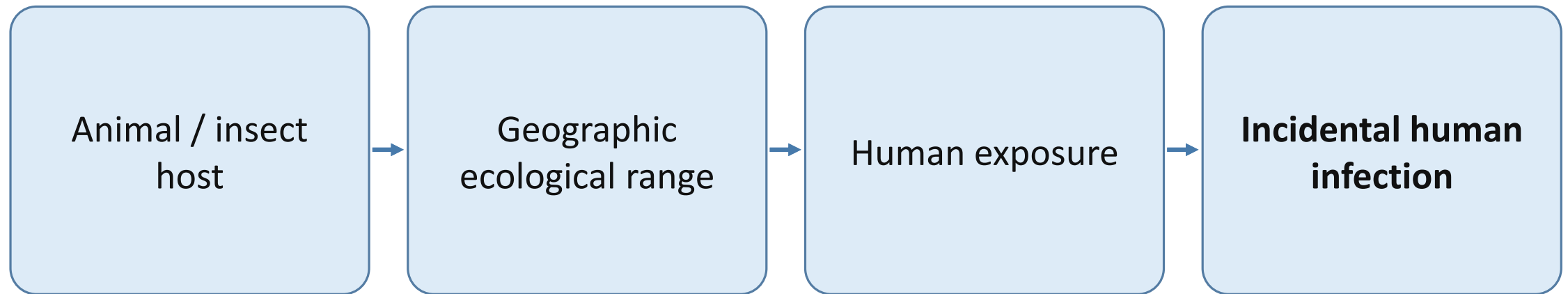
Four groups are highlighted by Robbins.

- Arenaviridae
- Filoviridae
- Bunyavirales
- Flaviviridae

Four viral groups: An etiologic orientation

Group named by Robbins	Anchor example or context	Teaching distinction
Arenaviridae	Lassa virus	Contact-associated spread may occur
Filoviridae	Ebola, Marburg	Prominent outbreaks and immune evasion
Bunyavirales	Crimean–Congo fever	Hemorrhagic phenotype can be prominent
Flaviviridae	Dengue	Severe disease includes plasma leakage

Reservoir and vector ecology shape incidence



Geographic risk follows the distribution of relevant hosts or vectors

Humans are usually incidental hosts

Natural cycle

- Virus circulates through animal or insect hosts.
- Host distribution constrains potential exposure.

Human infection

- Exposure to an infected host or vector.
- Clinical disease may emerge after spillover.

Rodents and bats are named animal exposures

- Rodents and bats as typical infected animal hosts.
- Animal exposure represents one pathway to human infection.
- The importance of a given host depends on the particular virus.

Mosquitoes and ticks are vector exposures

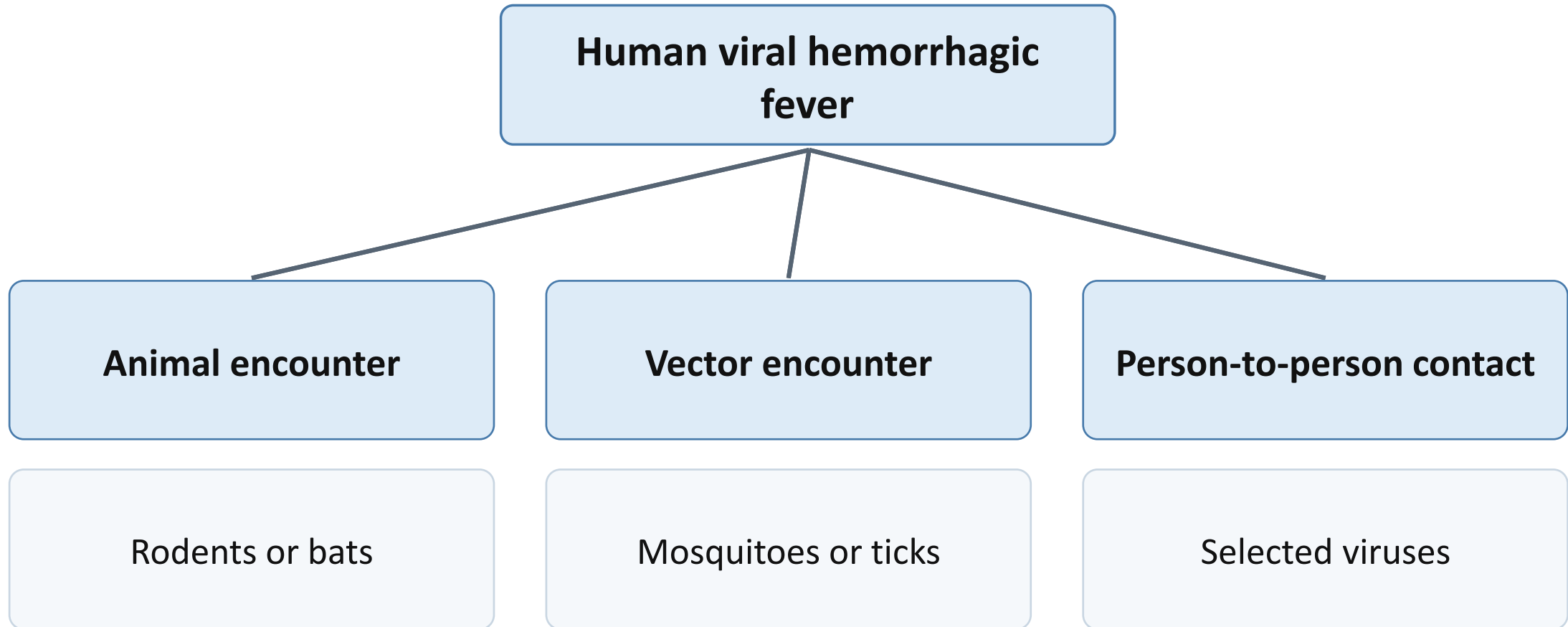
Mosquito-associated exposure

- Infection through an infected mosquito vector
- Dengue: Aedes mosquitoes

Tick-associated exposure

- Infection through an infected tick vector
- Not all hemorrhagic fever viruses share this route

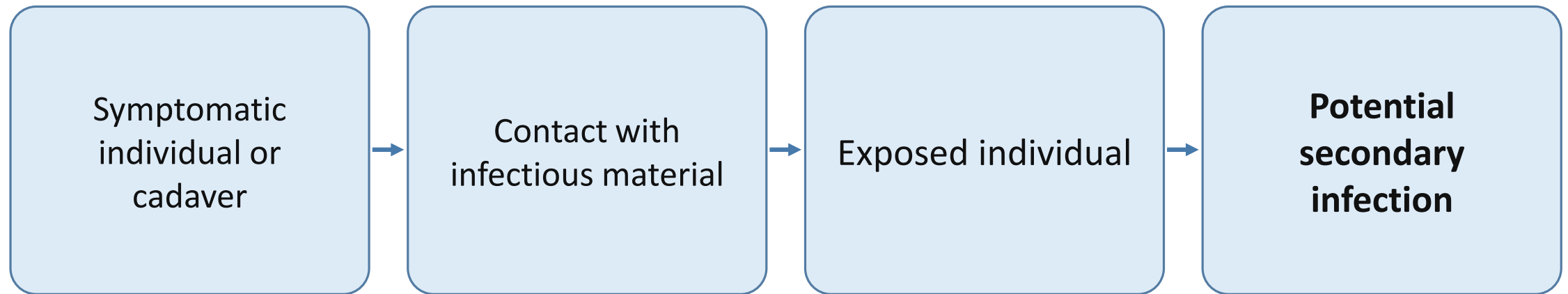
One label encompasses distinct exposure routes



Selected viruses spread between people

- Lassa virus
- Crimean–Congo hemorrhagic fever virus
- Ebola virus
- Marburg virus

Transmission can occur through contact



Person-to-person spread is documented for selected viruses only

Exposure history is mechanistically informative

Ecology-linked infection

- Animal or arthropod exposure
- Risk reflects host range
- Humans often incidental

Contact-linked infection

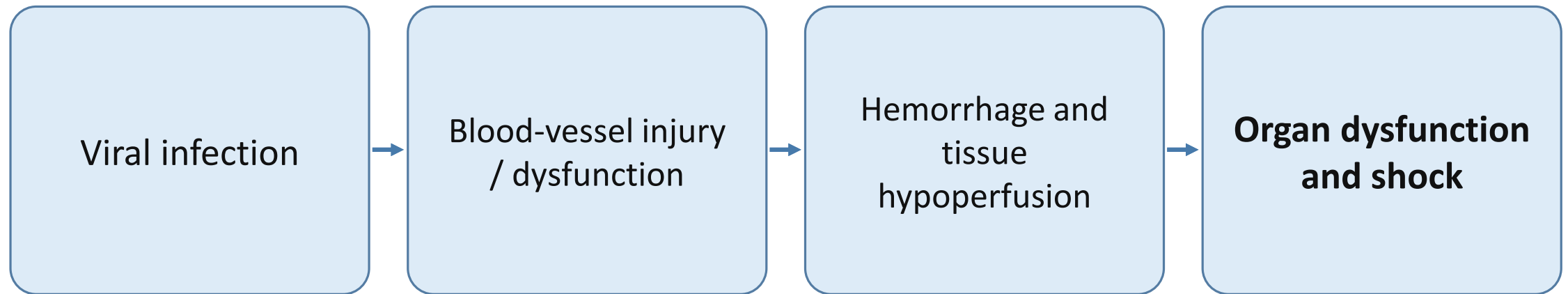
- Symptomatic cases / cadavers
- Secondary spread possible
- Outbreak amplification possible

The same syndrome can arise by different mechanisms

Do not equate hemorrhage with a unique pathogen.

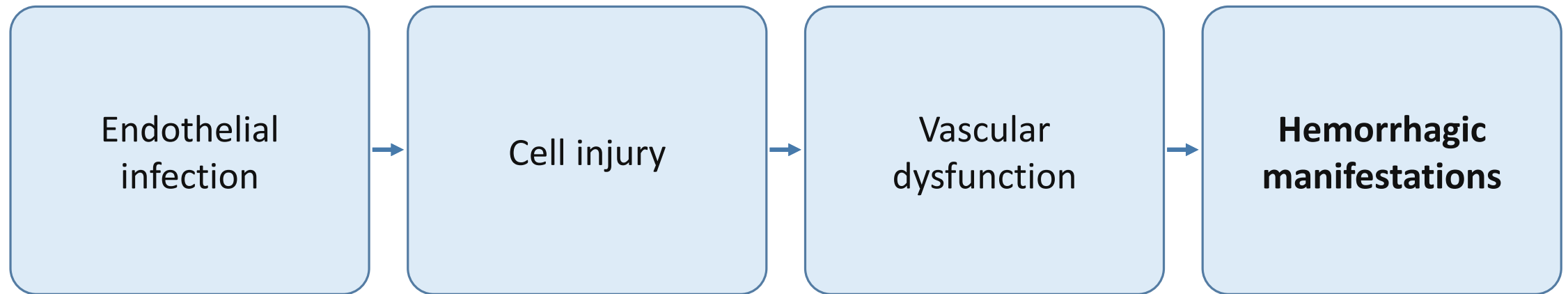
- Virologic etiology must be distinguished from the clinical syndrome.
- Exposure context helps organize the differential.
- Overlapping manifestations do not prove identical tissue injury.

Vascular injury is a central pathologic event



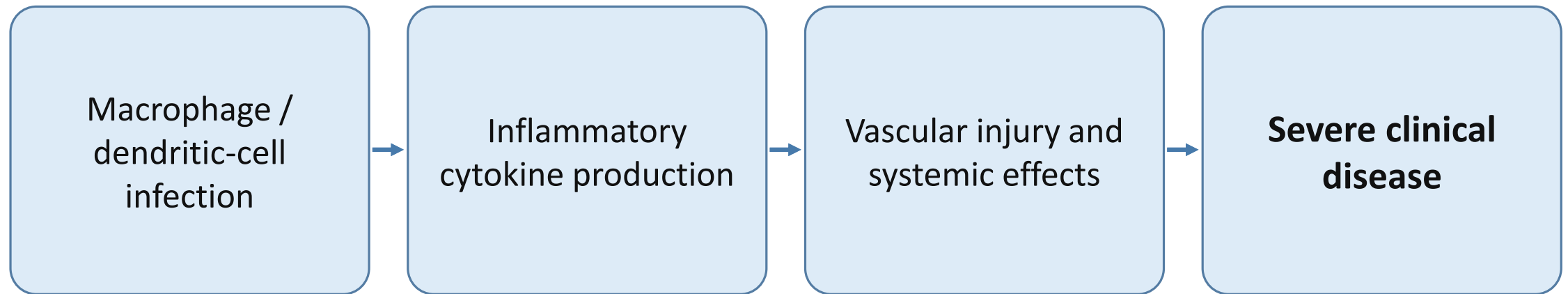
Conceptual causal chain; Relative contributions vary by virus

One pathway: Direct endothelial injury



Direct injury is one mechanism discussed by Robbins

A second pathway: Infected immune cells



Immune-cell-mediated injury is an alternative, not an exclusive route

Direct and cytokine-mediated pathways converge

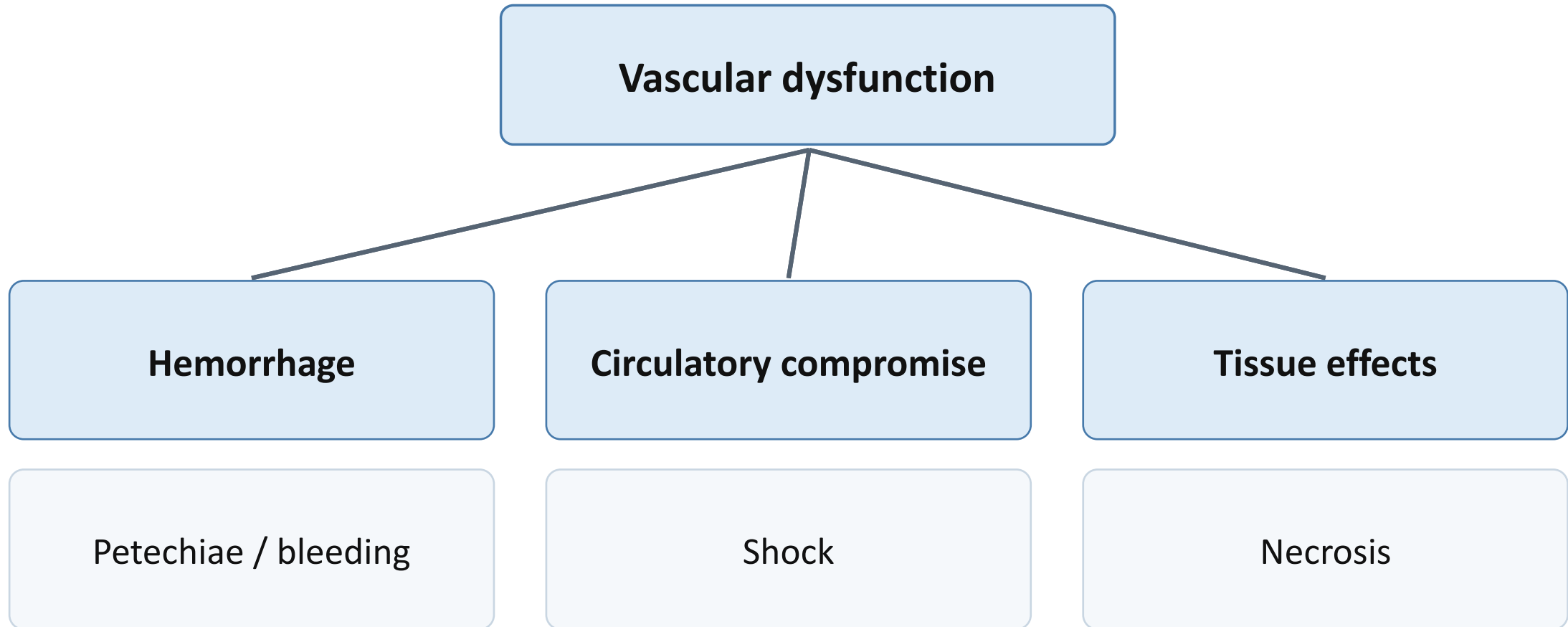
Direct route

- Endothelial infection
- Direct cell injury
- Vascular damage

Indirect route

- Macrophage or dendritic-cell infection
- Inflammatory cytokines
- Vascular damage

Vascular injury links mechanism to phenotype



Immune-mediated tissue damage is a general principle

- A host immune response may contribute to pathology as it attempts to control infection.
- Cytokine-mediated inflammation is one mechanism of systemic injury.
- In hemorrhagic fevers, infected macrophages and dendritic cells can participate in vascular damage.

Clinical severity differs among infections

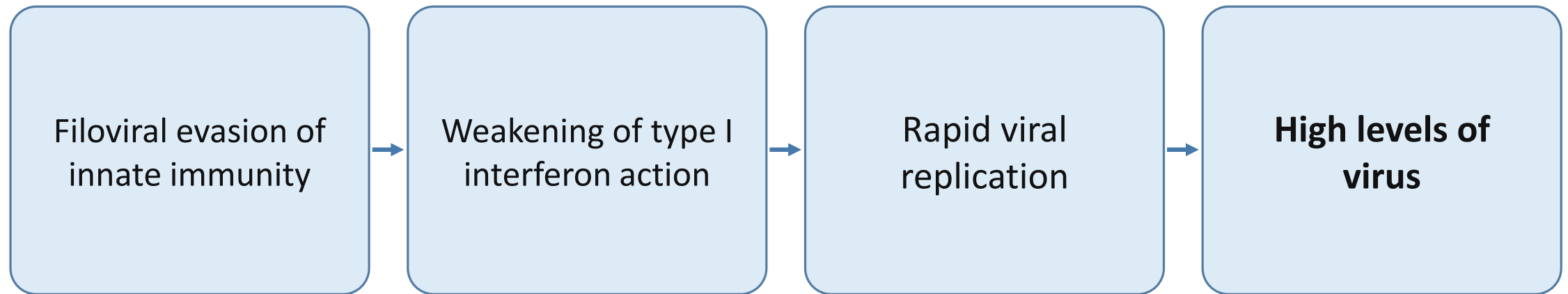
Common features

- Vascular abnormalities
- Hematologic derangements
- Potential shock

Virus-specific variation

- Dominant mechanism of injury
- Prominence of hemorrhage
- Extent and distribution of necrosis

Ebola: Immune evasion promotes high viral burden



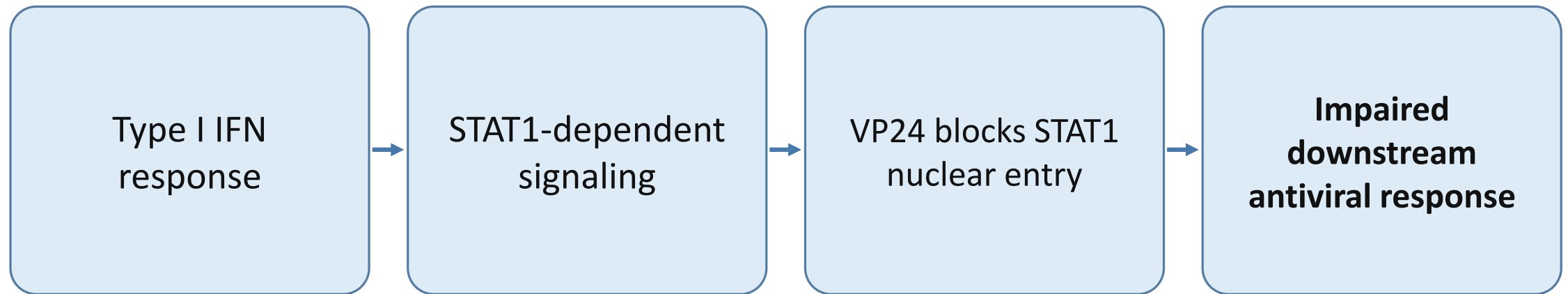
VP24 and VP35 as mechanistic examples

Type I interferon is the targeted antiviral axis

Viral proteins VP24 and VP35 interfere with type I IFN defenses.

- Interferon-dependent responses are part of antiviral host defense.
- Ebola inhibits steps in signaling and virus sensing.
- The outcome favors ongoing viral replication.

VP24 interferes with STAT1 nuclear translocation



Functional mechanism reported for Ebola VP24

STAT1 localization matters to signaling

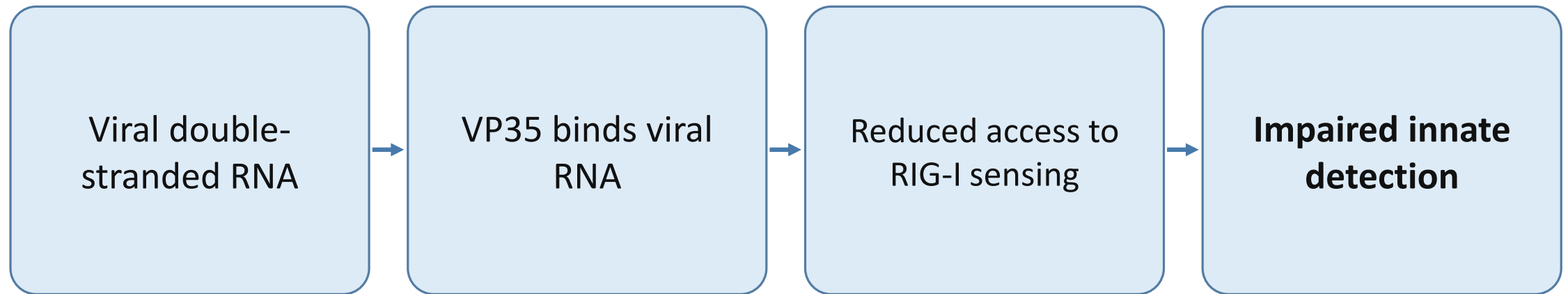
Intact response: Conceptual

- STAT1 reaches the nucleus
- Interferon-responsive gene expression can proceed

VP24 interference

- STAT1 nuclear translocation is inhibited
- Interferon-responsive signaling is blunted

VP35 conceals double-stranded viral RNA



Cytoplasmic viral RNA recognition is impeded

RIG-I is an RNA-sensing receptor

RIG-I helps detect viral RNA in the cytoplasm.

- RIG-I as a detector bypassed by VP35.
- Binding of viral RNA by VP35 prevents recognition.
- Impaired sensing favors immune evasion.

VP35 also inhibits interferon signaling

VP35: Sensing level

- Binds double-stranded viral RNA
- Prevents cytoplasmic RIG-I detection

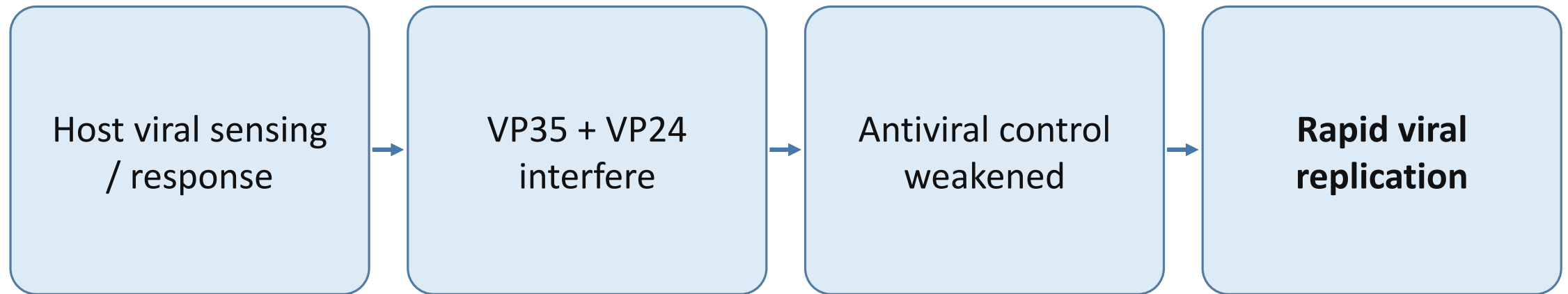
VP35: Response level

- Inhibits type I IFN signaling
- Adds a second level of immune evasion

VP24 and VP35 act at distinct checkpoints

Viral protein	Target or process	Functional consequence
VP24	STAT1 nuclear translocation	Blunted IFN-driven response
VP35	Double-stranded viral RNA	Reduced RIG-I detection
VP35	Type I IFN signaling	Additional signaling inhibition

Combined immune evasion explains replication



Mechanistic interpretation drawn description

Virulence is not synonymous with one lesion

- Ebola combines immune evasion with disseminated viral replication.
- Vascular damage can reflect infected cells and host-derived cytokines.
- Clinical deterioration results from multiple converging pathologic effects.

Early symptoms reflect a nonspecific viral illness

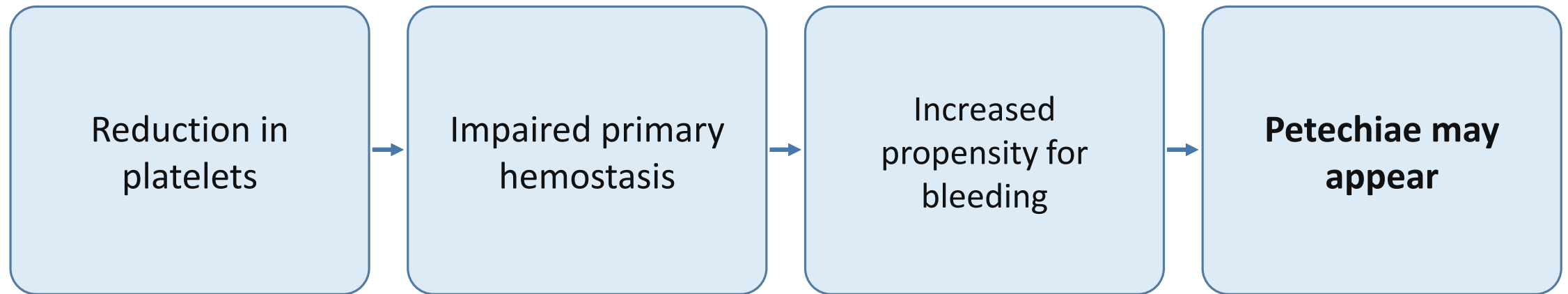
- Fever and headache
- Myalgia and rash
- Neutropenia and thrombocytopenia

Neutropenia is part of the described spectrum

A low neutrophil count may accompany early illness.

- The finding is not specific for a hemorrhagic-fever pathogen.
- Interpret it alongside exposure, symptoms and other cytopenias.
- Its presence alone does not establish severe disease.

Thrombocytopenia links clinical and bleeding biology



One contributor—not a sufficient explanation for all hemorrhage

Deterioration may be abrupt

Initially apparent

- Febrile illness
- Myalgia, rash
- Hematologic abnormalities

Potential subsequent deterioration

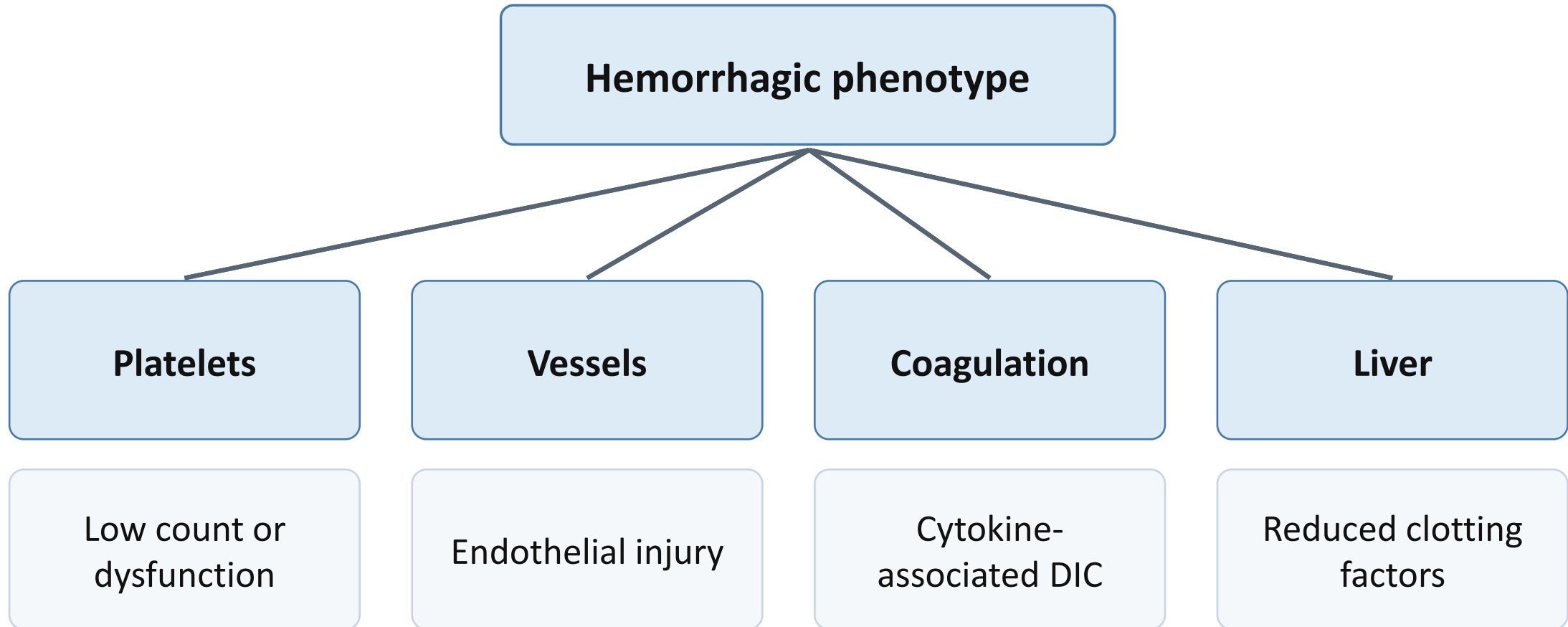
- Sudden hemodynamic decline
- Shock
- Organ damage

Shock reflects major circulatory compromise

Hemorrhagic fever can progress to shock.

- Shock as a severe syndrome outcome.
- Vascular damage and systemic injury are proximal pathologic themes.
- Bleeding alone does not account for every hemodynamic effect.

Hemorrhage has four interacting contributors



A low platelet count is only one mechanism

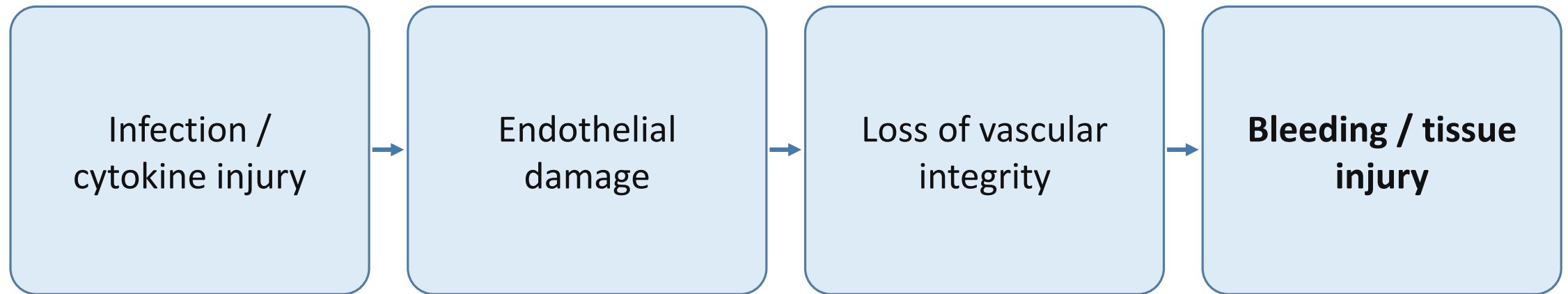
Quantitative defect

- Thrombocytopenia
- Fewer available platelets

Functional defect

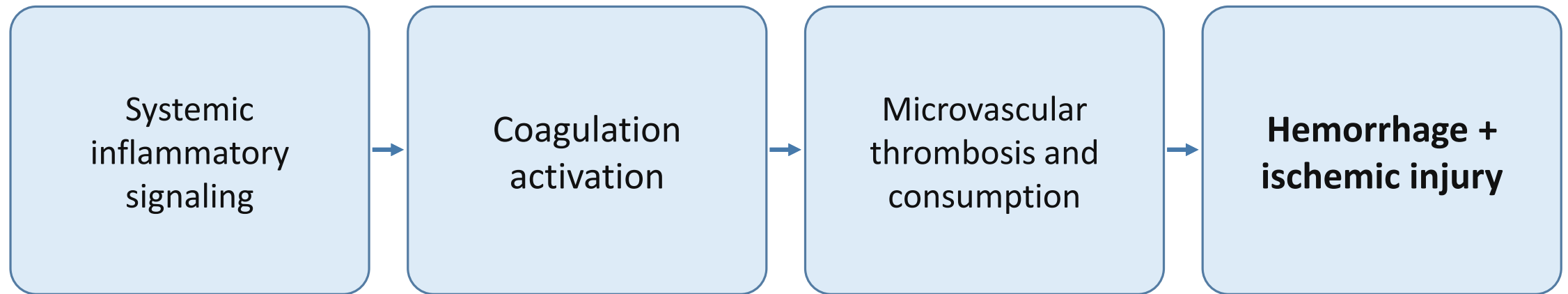
- Platelet dysfunction
- Ineffective hemostatic activity

Endothelial injury adds a vascular component



Injury can coexist with platelet and coagulation abnormalities

Cytokine-induced DIC can amplify bleeding



DIC is a systemic thrombohemorrhagic complication

DIC combines thrombosis and consumption

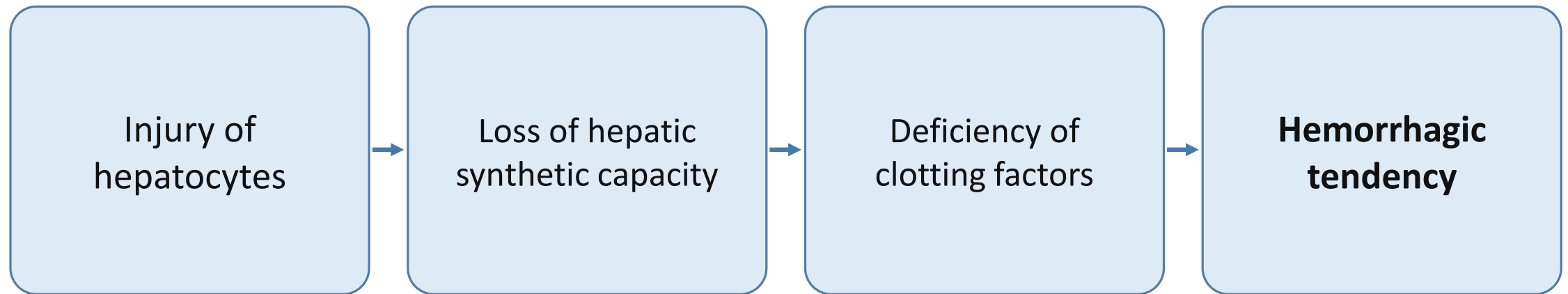
Microvascular thrombosis

- Small-vessel thrombi
- Reduced tissue perfusion
- Organ injury

Consumptive coagulopathy

- Platelets and factors depleted
- Secondary fibrinolysis
- Bleeding tendency

Hepatic necrosis can worsen coagulopathy



Hepatic injury as a source of factor deficiency

Bleeding is therefore multifactorial

Pathologic driver	Immediate consequence	Clinical correlate
Thrombocytopenia / dysfunction	Impaired platelet hemostasis	Petechiae / bleeding
Endothelial injury	Vascular damage	Hemorrhages
Cytokine-induced DIC	Factor / platelet consumption	Thrombohemorrhagic state
Hepatic injury	Factor deficiency	Coagulopathy

Petechiae are a recognizable manifestation

Petechiae may reflect several concurrent lesions.

- Platelet depletion or dysfunction
- Endothelial injury
- Coagulopathy associated with DIC or hepatic damage

Extent of bleeding varies by infection

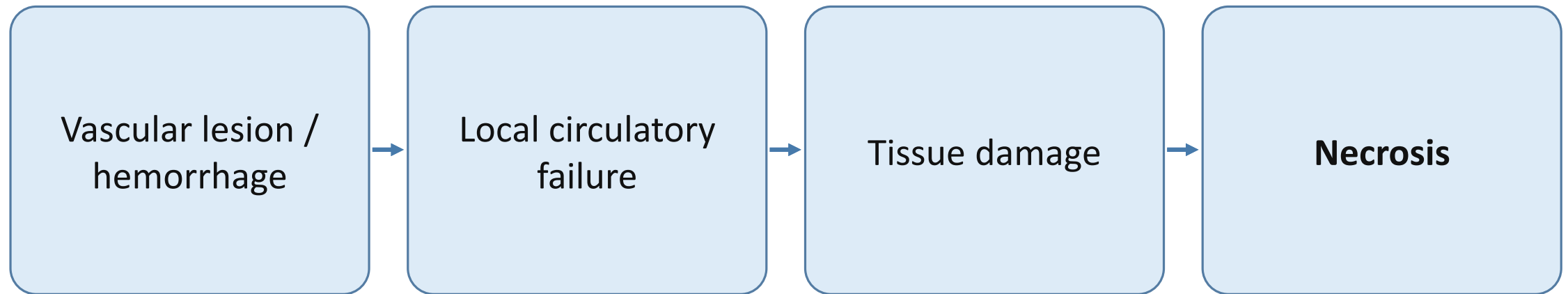
Prominent hemorrhage

- Can be conspicuous in Crimean–Congo fever
- Part of the pathologic phenotype

Severity interpretation

- Visible hemorrhage may not be life-threatening
- Overall risk also reflects shock and organ dysfunction

Tissue necrosis can follow vascular injury



Necrosis ranges from focal to massive across infections

Necrotic extent and inflammation can diverge

Extent of necrosis

- Mild and focal
- Or extensive / massive

Inflammatory reaction

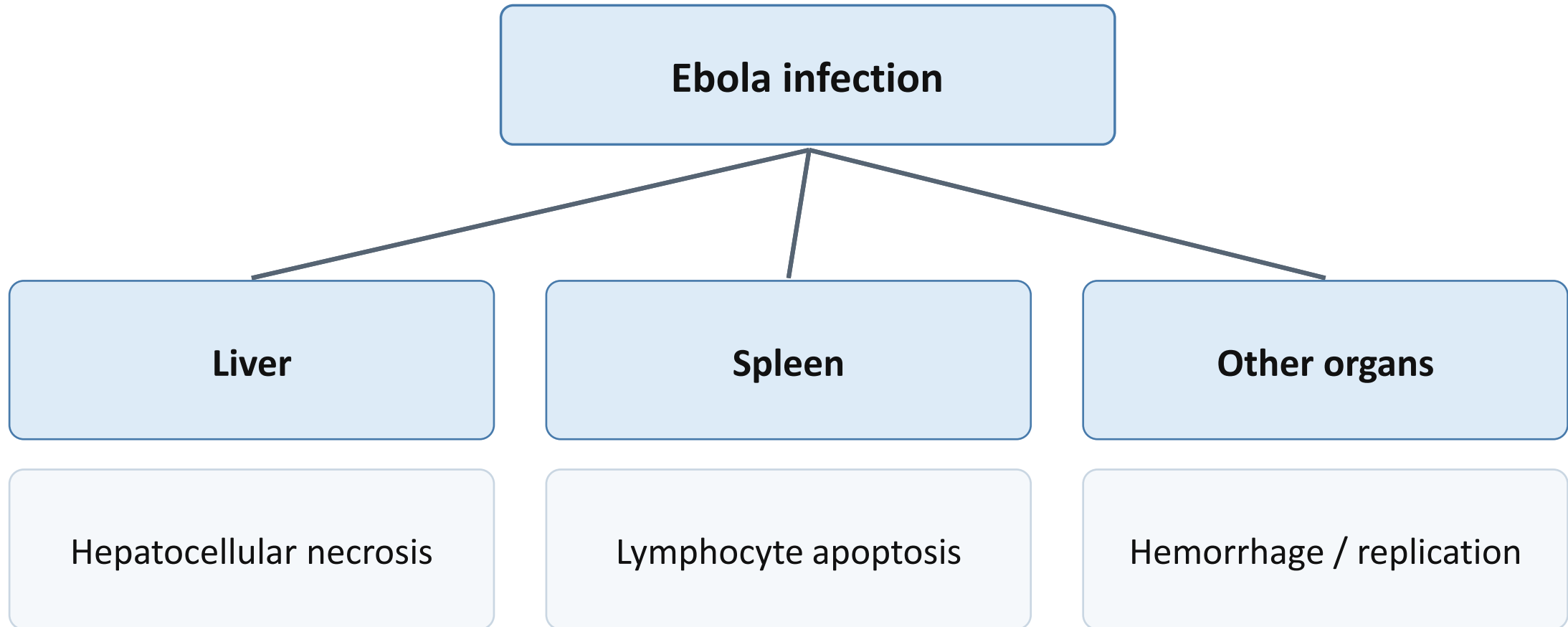
- Often unexpectedly minimal
- Do not equate scant inflammation with minor injury

The pathology can be severe but paucicellular

Marked tissue damage may occur with little inflammation.

- Necrosis is sometimes widespread.
- The accompanying inflammatory infiltrate is often scant.
- This dissociation is emphasized in Ebola virus infection.

Ebola demonstrates multiorgan viral replication



Liver morphology: Hepatocellular necrosis

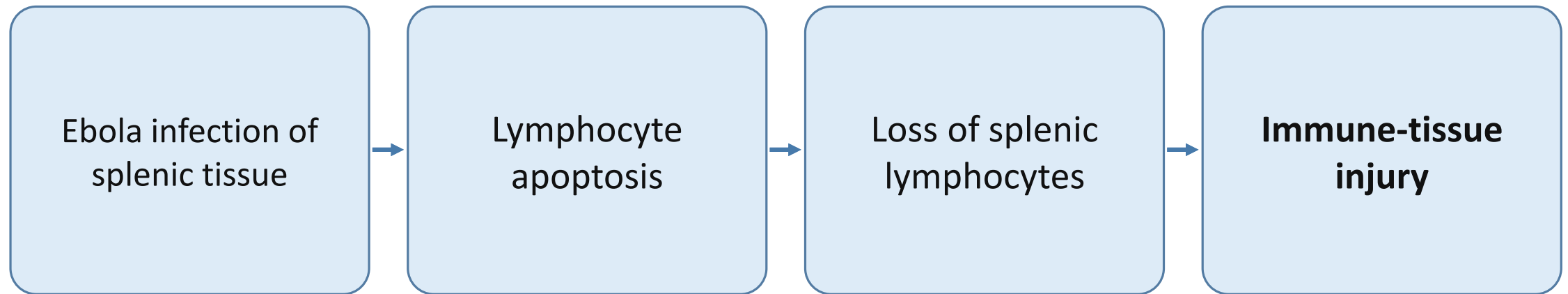
Liver injury

- Viral replication in the organ
- Hepatocellular necrosis

Histologic reaction

- Relatively scant inflammation
- Hepatic injury may aggravate coagulopathy

Spleen morphology: Lymphocyte apoptosis



Pathologic association in Ebola infection; Not a quantitative cell-count model

Splenic viral replication involves several cells

Cell population	Source-described finding
Dendritic cells	Viral replication
Fibroblasts	Viral replication
Monocytes	Viral replication
Lymphocytes	Apoptosis

Liver and spleen show different dominant lesions

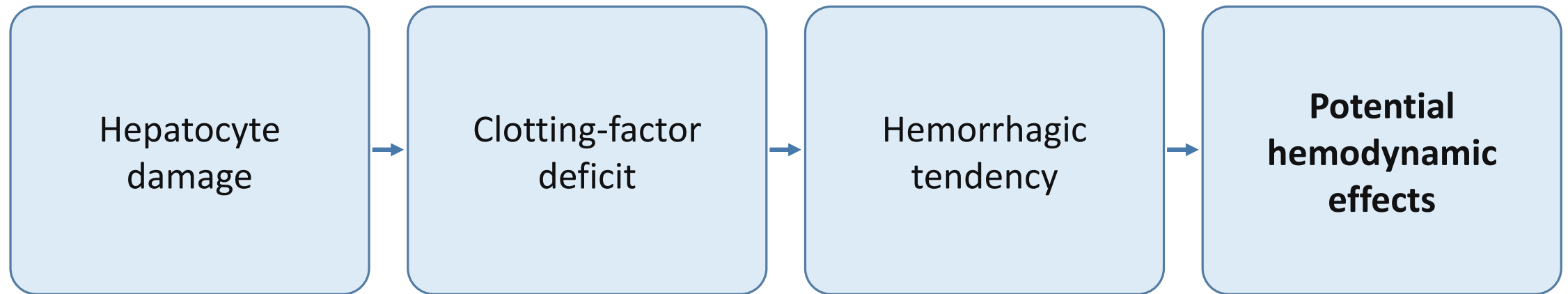
Liver

- Hepatocyte necrosis
- Scant inflammation
- Coagulation-factor deficiency may follow

Spleen

- Lymphocyte apoptosis
- Virus in dendritic cells, fibroblasts and monocytes
- Immune-system injury

Microscopy helps explain systemic consequences



Morphology-to-physiology inference, paired with documented hepatic injury

Ebola caused a major West African outbreak

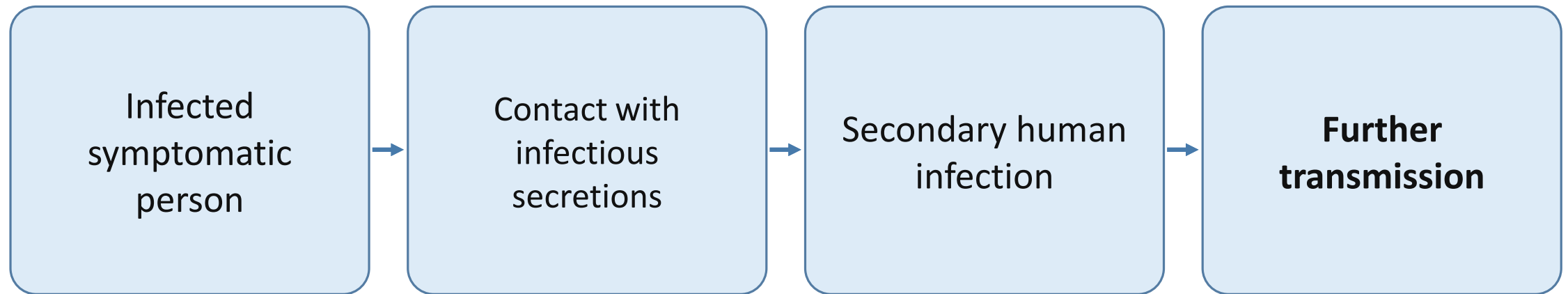
2014–2016: Sierra Leone, Liberia and Guinea.

- This as a major Ebola outbreak.
- Human-to-human transmission drove rapid spread.
- Historical outbreak context—not a present-day surveillance update.

The 2014–2016 outbreak burden was substantial

Robbins-reported historical metric	Value
Cases reported to WHO	More than 28,000
Deaths reported to WHO	More than 11,000

Ebola transmission can amplify an outbreak



Explosive outbreak spread to person-to-person exposure

Further Ebola outbreaks occurred in DRC

- Several outbreaks in the Democratic Republic of Congo since 2017.
- The outbreak pattern underscores the relevance of person-to-person contact.
- This is historical source context; No current outbreak claim is implied.

Ebola mortality varies across outbreaks

Approximately 40% mortality during a 2019 outbreak.

- This figure is specific to the cited historical outbreak.
- It should not be generalized to every filovirus or setting.
- Mortality is distinct from the frequency or volume of hemorrhage.

Ebola vaccines were used in outbreak control

- Effective Ebola vaccines had been developed by the time covered.
- The text notes deployment during outbreaks in Guinea and the Democratic Republic of Congo.
- The source does not supply a current vaccination schedule or product-specific policy.

Case application: Ebola pathology

A fatal febrile illness has hemorrhage, hepatocyte necrosis with little inflammation, and splenic lymphocyte apoptosis.

Which viral syndrome and two key tissue processes are most strongly suggested?

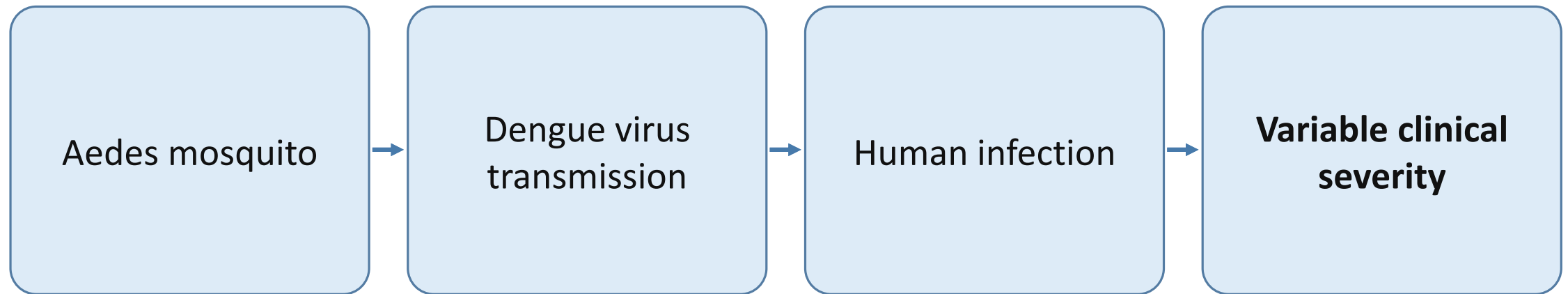
Interpretation: Ebola-associated hemorrhagic fever; Hepatocellular necrosis and splenic lymphocyte apoptosis.

Dengue broadens the hemorrhagic-fever spectrum

Severe dengue can cause hemorrhage, plasma leakage and organ failure.

- Dengue is an Aedes-transmitted flavivirus.
- Clinical illness ranges from fever to severe disease.
- The severe phenotype is not mechanistically identical to Ebola.

Dengue transmission is mosquito-associated



Robbins additionally notes less common prenatal/perinatal and transfusion routes

Most dengue illness is not severe dengue

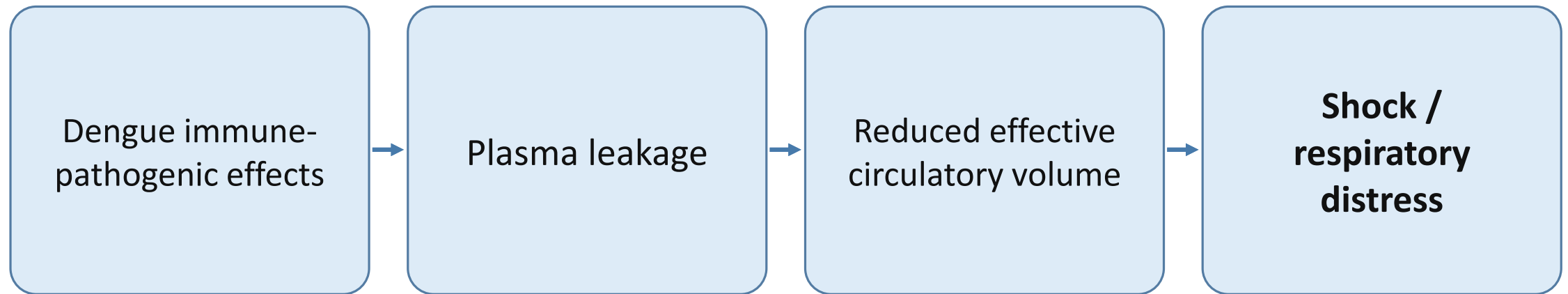
Common dengue illness

- Fever and headache
- Macular rash
- Severe myalgia (“breakbone fever”)

Severe dengue

- Bleeding / hepatitis
- Plasma leakage and shock
- Organ failure / respiratory distress

Severe dengue involves vascular leakage

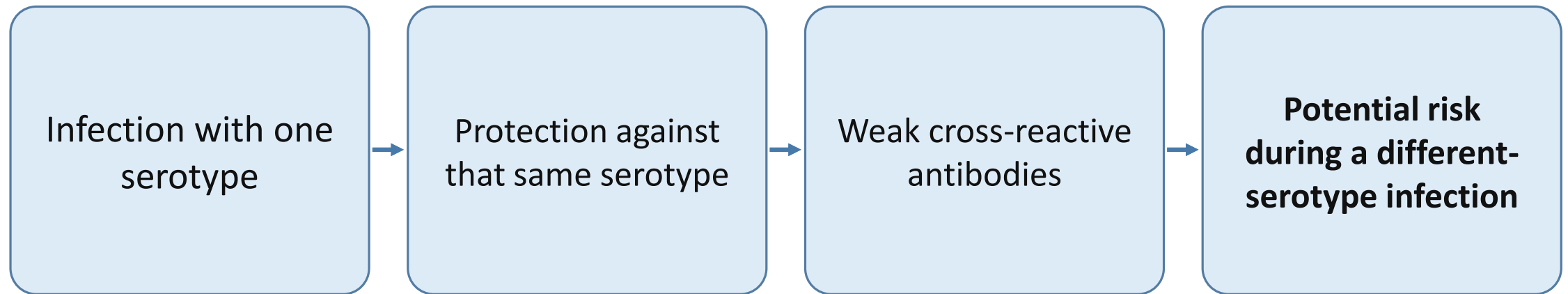


Severe dengue mechanism

Severe dengue has identifiable organ lesions

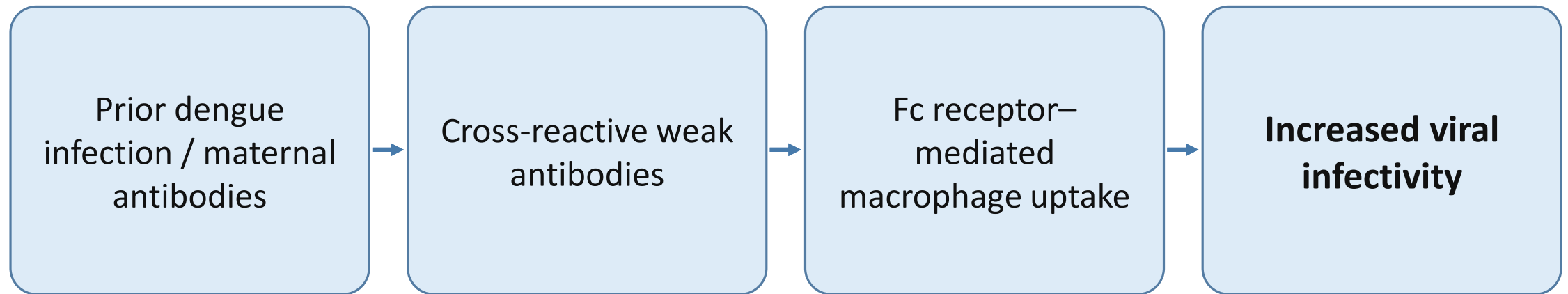
Organ or compartment	Reported pathologic consequence
Circulation	Plasma leakage / shock
Liver	Hepatitis or liver failure
Lung	Diffuse alveolar damage with hyaline membranes
Multiple organs	Widespread hemorrhages / dysfunction

Four dengue serotypes complicate immunity



Cross-reactive response is not reliably protective

Antibody-dependent enhancement is a proposed mechanism



Antibody-dependent enhancement (ADE) as a contributing model

Severe dengue is linked to heterotypic immunity

Prior same-serotype infection

- Protective serotype-specific immunity
- Not the classic ADE scenario

Different-serotype exposure

- Weak cross-reactive antibodies
- Can promote Fc-receptor uptake
- Higher risk of severe dengue

Maternal antibodies support the ADE model

- Severe dengue also occurs in infants with maternal dengue antibodies.
- This clinical observation is consistent with antibody-dependent enhancement.
- The model remains a partial explanation of heterogeneous dengue severity.

Dengue and Ebola differ in emphasis

Dimension	Ebola	Severe dengue
Agent group	Filoviridae	Flaviviridae
Highlighted immune mechanism	VP24 / VP35 interferon evasion	Cross-reactive antibody enhancement
Highlighted organ injury	Liver necrosis; splenic apoptosis	Hepatitis; alveolar damage
Relevant transmission	Human contact possible	Aedes mosquito vector

Case application: Severe dengue

A patient with previous dengue infection develops fever, vascular leakage and shock after infection by a different dengue serotype.

What antibody-mediated mechanism is proposed to contribute to this severity?

Interpretation: Weak cross-reactive antibodies can facilitate Fc receptor–mediated uptake by macrophages (ADE).

Mechanism-to-morphology review

Initiating mechanism	Pathologic effect	Clinical implication
Endothelial / cytokine injury	Vascular damage	Hemorrhage, shock
DIC / factor depletion	Hemostatic failure	Bleeding tendency
Ebola hepatocyte infection	Necrosis with scant inflammation	Organ injury / factor deficiency
Heterotypic dengue immunity	Enhanced macrophage uptake (proposed)	Risk of severe dengue

Three distinctions to retain

- A shared hemorrhagic phenotype does not imply a shared route of transmission.
- Visible bleeding is only one consequence of vascular and systemic injury.
- Ebola interferon evasion and dengue ADE describe different immune-pathogenic mechanisms.

Source references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 8: Infectious Diseases, pp. 318–320.

Robbins, Cotran & Kumar. Chapter 8: Mechanisms of Viral Injury, p. 308.

Robbins, Cotran & Kumar. Chapter 4: Disseminated Intravascular Coagulation, p. 114; Chapter 14: Red Blood Cell and Bleeding Disorders, p. 608.